

=> fil lreg  
FILE 'LREGISTRY' ENTERED AT 16:25:43 ON 11 OCT 2005  
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.  
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.  
COPYRIGHT (C) 1985 AMERICAN CHEMICAL SOCIETY (ACS)

LREGISTRY IS A STATIC LEARNING FILE

NEW CAS INFORMATION USE POLICIES, ENTER HELP USAGETERMS FOR DETAILS.

=> fil reg  
FILE 'REGISTRY' ENTERED AT 16:25:45 ON 11 OCT 2005  
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.  
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.  
COPYRIGHT (C) 2005 American Chemical Society (ACS)

Property values tagged with IC are from the ZIC/VINITI data file  
provided by InfoChem.

STRUCTURE FILE UPDATES: 10 OCT 2005 HIGHEST RN 864908-12-3  
DICTIONARY FILE UPDATES: 10 OCT 2005 HIGHEST RN 864908-12-3

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH JULY 14, 2005

Please note that search-term pricing does apply when  
conducting SmartSELECT searches.

\*\*\*\*\*  
\*  
\* The CA roles and document type information have been removed from \*  
\* the IDE default display format and the ED field has been added, \*  
\* effective March 20, 2005. A new display format, IDERL, is now \*  
\* available and contains the CA role and document type information. \*  
\*  
\*\*\*\*\*

Structure search iteration limits have been increased. See HELP SLIMITS  
for details.

REGISTRY includes numerically searchable data for experimental and  
predicted properties as well as tags indicating availability of  
experimental property data in the original document. For information  
on property searching in REGISTRY, refer to:

<http://www.cas.org/ONLINE/UG/regprops.html>

=> fil zcap  
FILE 'ZCAPLUS' ENTERED AT 16:25:48 ON 11 OCT 2005  
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.  
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.  
COPYRIGHT (C) 2005 AMERICAN CHEMICAL SOCIETY (ACS)

Copyright of the articles to which records in this database refer is  
held by the publishers listed in the PUBLISHER (PB) field (available  
for records published or updated in Chemical Abstracts after December  
26, 1996), unless otherwise indicated in the original publications.  
The CA Lexicon is the copyrighted intellectual property of the

American Chemical Society and is provided to assist you in searching databases on STN. Any dissemination, distribution, copying, or storing of this information, without the prior written consent of CAS is strictly prohibited.

FILE COVERS 1907 - 11 Oct 2005 VOL 143 ISS 16  
FILE LAST UPDATED: 10 Oct 2005 (20051010/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> fil hcap  
FILE 'HCAPLUS' ENTERED AT 16:25:51 ON 11 OCT 2005  
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.  
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.  
COPYRIGHT (C) 2005 AMERICAN CHEMICAL SOCIETY (ACS)

Copyright of the articles to which records in this database refer is held by the publishers listed in the PUBLISHER (PB) field (available for records published or updated in Chemical Abstracts after December 26, 1996), unless otherwise indicated in the original publications. The CA Lexicon is the copyrighted intellectual property of the American Chemical Society and is provided to assist you in searching databases on STN. Any dissemination, distribution, copying, or storing of this information, without the prior written consent of CAS, is strictly prohibited.

FILE COVERS 1907 - 11 Oct 2005 VOL 143 ISS 16  
FILE LAST UPDATED: 10 Oct 2005 (20051010/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> fil uspatfull  
FILE 'USPATFULL' ENTERED AT 16:25:58 ON 11 OCT 2005  
CA INDEXING COPYRIGHT (C) 2005 AMERICAN CHEMICAL SOCIETY (ACS)

FILE COVERS 1971 TO PATENT PUBLICATION DATE: 6 Oct 2005 (20051006/PD)  
FILE LAST UPDATED: 6 Oct 2005 (20051006/ED)  
HIGHEST GRANTED PATENT NUMBER: US6952836  
HIGHEST APPLICATION PUBLICATION NUMBER: US2005223461  
CA INDEXING IS CURRENT THROUGH 6 Oct 2005 (20051006/UPCA)  
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 6 Oct 2005 (20051006/PD)  
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Aug 2005  
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Aug 2005

>>> USPAT2 is now available. USPATFULL contains full text of the <<<  
>>> original, i.e., the earliest published granted patents or <<<  
>>> applications. USPAT2 contains full text of the latest US <<<  
>>> publications, starting in 2001, for the inventions covered in <<<  
>>> USPATFULL. A USPATFULL record contains not only the original <<<  
>>> published document but also a list of any subsequent <<<  
>>> publications. The publication number, patent kind code, and <<<  
>>> publication date for all the US publications for an invention <<<  
>>> are displayed in the PI (Patent Information) field of USPATFULL <<<

```
>>> records and may be searched in standard search fields, e.g., /PN, <<<
>>> /PK, etc. <<<

>>> USPATFULL and USPAT2 can be accessed and searched together <<<
>>> through the new cluster USPATALL. Type FILE USPATALL to <<<
>>> enter this cluster. <<<

>>>
>>> Use USPATALL when searching terms such as patent assignees, <<<
>>> classifications, or claims, that may potentially change from <<<
>>> the earliest to the latest publication. <<<
```

This file contains CAS Registry Numbers for easy and accurate substance identification.

```
=> fil uspat2
FILE 'USPAT2' ENTERED AT 16:26:02 ON 11 OCT 2005
CA INDEXING COPYRIGHT (C) 2005 AMERICAN CHEMICAL SOCIETY (ACS)
```

```
FILE COVERS 2001 TO PUBLICATION DATE: 11 Oct 2005 (20051011/PD)
FILE LAST UPDATED: 11 Oct 2005 (20051011/ED)
HIGHEST GRANTED PATENT NUMBER: US2005054189
HIGHEST APPLICATION PUBLICATION NUMBER: US2005222704
CA INDEXING IS CURRENT THROUGH 11 Oct 2005 (20051011/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 11 Oct 2005 (20051011/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Aug 2005
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Aug 2005
```

USPAT2 is a companion file to USPATFULL. USPAT2 contains full text of the latest US publications, starting in 2001, for the inventions covered in USPATFULL. USPATFULL contains full text of the original published US patents from 1971 to date and the original applications from 2001. In addition, a USPATFULL record for an invention contains a complete list of publications that may be searched in standard search fields, e.g., /PN, /PK, etc.

USPATFULL and USPAT2 can be accessed and searched together through the new cluster USPATALL. Type FILE USPATALL to enter this cluster.

Use USPATALL when searching terms such as patent assignees, classifications, or claims, that may potentially change from the earliest to the latest publication.

```
=> fil toxcenter
FILE 'TOXCENTER' ENTERED AT 16:26:06 ON 11 OCT 2005
COPYRIGHT (C) 2005 ACS
```

```
FILE COVERS 1907 TO 11 Oct 2005 (20051011/ED)
```

This file contains CAS Registry Numbers for easy and accurate substance identification.

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TOXCENTER has been enhanced with new files segments and search fields. See HELP CONTENT for more information.

TOXCENTER thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2005 vocabulary. See <http://www.nlm.nih.gov/mesh/> and

[http://www.nlm.nih.gov/pubs/techbull/nd04/nd04\\_mesh.html](http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html) for a description of changes.

=> fil beilstein  
FILE 'BEILSTEIN' ENTERED AT 16:26:11 ON 11 OCT 2005  
COPYRIGHT (c) 2005 Beilstein-Institut zur Foerderung der Chemischen Wissenschaften licensed to Beilstein GmbH and MDL Information Systems GmbH

FILE RELOADED ON OCTOBER 20, 2002  
FILE LAST UPDATED ON JUNE 29, 2005

FILE COVERS 1771 TO 2005.  
\*\*\* FILE CONTAINS 9,271,550 SUBSTANCES \*\*\*

>>> PLEASE NOTE: Reaction Data and substance data are stored in separate documents and can not be searched together in one query. Reaction data for BEILSTEIN compounds may be displayed immediately with the display codes PRE (preparations) and REA (reactions). A substance answer set retrieved after the search for a chemical name, a compounds with available reaction information by combining with PRE/FA, REA/FA or more generally with RX/FA. The BEILSTEIN Registry Number (BRN) is the link between a BEILSTEIN compound and belonging reactions. For more detailed reaction searches BRNs can be searched as reaction partner BRNs Reactant BRN (RX.RBRN) or Product BRN (RX.PBRN). <<<

>>> FOR SEARCHING PREPARATIONS SEE HELP PRE <<<

\*\*\*\*\*  
\* PLEASE NOTE THAT THERE ARE NO FORMATS FREE OF COST. \*  
\* SET NOTICE FEATURE: THE COST ESTIMATES CALCULATED FOR SET NOTICE \*  
\* ARE BASED ON THE HIGHEST PRICE CATEGORY. THEREFORE; THESE \*  
\* ESTIMATES MAY NOT REFLECT THE ACTUAL COSTS. \*  
\* FOR PRICE INFORMATION SEE HELP COST \*  
\*\*\*\*\*

NEW  
\* PATENT NUMBERS (PN) AND BABS ACCESSION NUMBERS (BABSAN) CAN NOW BE SEARCHED, SELECTED AND TRANSFERRED.  
\* NEW DISPLAY FORMATS ALLREF, ALLP AND BABSAN SHOW ALL REFERENCES, ALL PATENT REFERENCES, OR ALL BABS ACCESSION NUMBERS FOR A COMPOUND AT A GLANCE.

=> fil chemcats  
FILE 'CHEMCATS' ENTERED AT 16:26:16 ON 11 OCT 2005  
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.  
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.  
COPYRIGHT (C) 2005 American Chemical Society (ACS)

FILE LAST UPDATED 08 OCTOBER 2005 (20051008/UP)

For details on recent updates in CHEMCATS, enter NEWS FILE at an arrow prompt. For the list of suppliers currently in the file, enter HELP SPA, HELP SPBC, HELP SPDH, HELP SPIN, HELP SPOP, and HELP SPQZ. For the list of current catalogs, enter HELP CTA, HELP CTBC, HELP CTDH, HELP CTIN, HELP CTOP, and HELP CTQZ.

This database is provided on an "as is" basis. Please consult the suppliers for current information regarding pricing, regional availability, available quantities, purities, etc. THERE ARE NO

WARRANTIES OF ANY KIND, EITHER EXPRESSED OR IMPLIED. ACS is not liable for any loss of profit, goodwill or any other damages arising out of the use of this database.

CHEMCATS now contains more than 8 million records. See HELP CONTENT and NEWS FILE for details.

```
=> file stnguide
FILE 'STNGUIDE' ENTERED AT 16:26:18 ON 11 OCT 2005
USE IS SUBJECT TO THE TERMS OF YOUR CUSTOMER AGREEMENT
COPYRIGHT (C) 2005 AMERICAN CHEMICAL SOCIETY, JAPAN SCIENCE
AND TECHNOLOGY CORPORATION, AND FACHINFORMATIONSZENTRUM KARLSRUHE
```

FILE CONTAINS CURRENT INFORMATION.  
LAST RELOADED: Oct 7, 2005 (20051007/UP).

=> d his 159

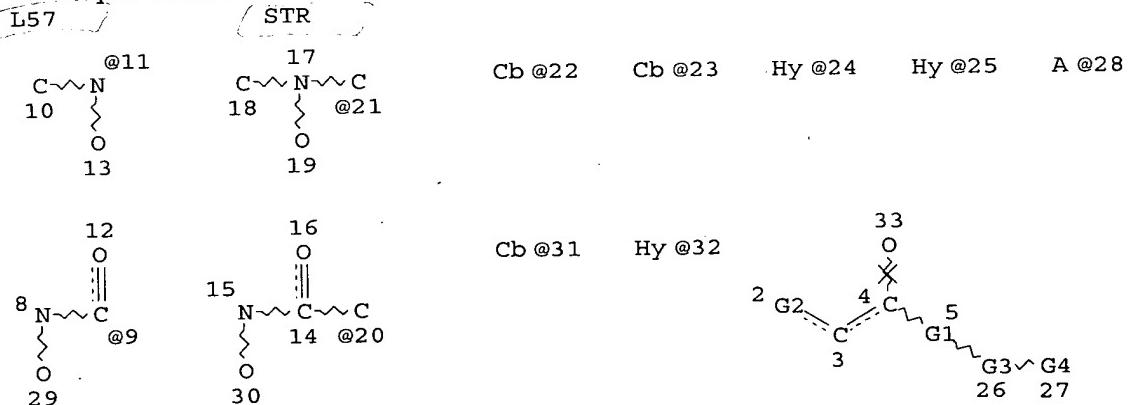
(FILE 'REGISTRY' ENTERED AT 15:30:49 ON 11 OCT 2005)

FILE 'STNGUIDE' ENTERED AT 15:31:00 ON 11 OCT 2005

FILE 'REGISTRY' ENTERED AT 15:35:36 ON 11 OCT 2005

L59 57 S L57 FUL

=> d que stat 159



VAR G1=22/23/24/25

VAR G2=9/11/20/21

REP G3=(2-20) 28

VAR G4=31/32

NODE ATTRIBUTES:

NSPEC	IS RC	AT	3
NSPEC	IS RC	AT	4
NSPEC	IS RC	AT	20
NSPEC	IS RC	AT	21
NSPEC	IS RC	AT	28
NSPEC	IS RC	AT	33
CONNECT	IS E2	RC AT	8
CONNECT	IS E1	RC AT	13
CONNECT	IS E2	RC AT	15
CONNECT	IS E1	RC AT	19
CONNECT	IS M2	RC AT	22
CONNECT	IS M2	RC AT	23

CONNECT IS M2 RC AT 24  
 CONNECT IS M2 RC AT 25  
 DEFAULT MLEVEL IS ATOM  
 GGCAT IS MCY UNS AT 22  
 GGCAT IS PCY UNS AT 23  
 GGCAT IS MCY UNS AT 24  
 GGCAT IS MCY UNS AT 25  
 DEFAULT ECLEVEL IS LIMITED  
 ECOUNT IS E6 C AT 22  
 ECOUNT IS E10 C AT 23  
 ECOUNT IS E5 C E1 N AT 24  
 ECOUNT IS E4 C E2 N AT 25  
 ECOUNT IS M3-X13 C AT 31  
 ECOUNT IS M1-X13 C AT 32

## GRAPH ATTRIBUTES:

RING(S) ARE ISOLATED OR EMBEDDED  
 NUMBER OF NODES IS 30

## STEREO ATTRIBUTES: NONE

L59 57 SEA FILE=REGISTRY SSS FUL L57

100.0% PROCESSED 65451 ITERATIONS  
 SEARCH TIME: 00.00.01

57 ANSWERS

=> d his 166

(FILE 'HCAPLUS, USPATFULL, USPAT2, TOXCENTER, BEILSTEIN, CHEMCATS'  
 ENTERED AT 16:23:16 ON 11 OCT 2005)  
 L66 26 DUP REM L65 (8 DUPLICATES REMOVED)  
 SAVE TEMP L66 HOF197MULS1/A  
 FILE 'STNGUIDE' ENTERED AT 16:24:51 ON 11 OCT 2005  
 FILE 'STNGUIDE' ENTERED AT 16:25:23 ON 11 OCT 2005  
 FILE 'LREGISTRY' ENTERED AT 16:25:43 ON 11 OCT 2005  
 FILE 'REGISTRY' ENTERED AT 16:25:45 ON 11 OCT 2005  
 FILE 'ZCAPLUS' ENTERED AT 16:25:48 ON 11 OCT 2005  
 FILE 'HCAPLUS' ENTERED AT 16:25:51 ON 11 OCT 2005  
 FILE 'USPATFULL' ENTERED AT 16:25:58 ON 11 OCT 2005  
 FILE 'USPAT2' ENTERED AT 16:26:02 ON 11 OCT 2005  
 FILE 'TOXCENTER' ENTERED AT 16:26:06 ON 11 OCT 2005  
 FILE 'BEILSTEIN' ENTERED AT 16:26:11 ON 11 OCT 2005  
 FILE 'CHEMCATS' ENTERED AT 16:26:16 ON 11 OCT 2005  
 FILE 'STNGUIDE' ENTERED AT 16:26:18 ON 11 OCT 2005

=> d que nos 166

L57 STR

L59 57 SEA FILE=REGISTRY SSS FUL L57  
L65 34 SEA L59  
I.66 26 DUP REM L65 (8 DUPLICATES REMOVED)

=> d 164  
 L64 ANALYZE L59 1- LC : 7 TERMS  
 TERM # # OCC # DOC % DOC LC  
 -----  
 1 56 56 98.25 CA  
 2 56 56 98.25 CAPLUS  
 3 52 52 91.23 USPATFULL  
 4 46 46 80.70 TOXCENTER  
 5 1 1 1.75 BEILSTEIN  
 6 1 1 1.75 CHEMCATS  
 7 1 1 1.75 USPAT2  
 \*\*\*\* END OF L64 \*\*\*

=> d ibib ed ab hitstr ind 166 1-  
YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS, USPATFULL, BEILSTEIN, CHEMCATS' --  
CONTINUE? (Y)/N:y

NO VALID FORMATS ENTERED FOR FILE 'CHEMCATS'  
In a multifile environment, each file must have at least one valid  
format requested. Refer to file specific help messages or the  
STNGUIDE file for information on formats available in individual  
files.

REENTER DISPLAY FORMAT FOR ALL FILES (FILEDEFAULT) :end

=> d 166 ibib ed ab ind hitstr retable 1-10  
YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS, USPATFULL, BEILSTEIN, CHEMCATS' -  
CONTINUE? (Y)/N:y

L66 ANSWER 1 OF 26 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 1  
ACCESSION NUMBER: 2004:120672 HCAPLUS  
DOCUMENT NUMBER: 140:177322  
TITLE: Hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNF $\alpha$  converting enzyme for use in treatment of diseases  
INVENTOR(S): Maduskuie, Thomas P.  
PATENT ASSIGNEE(S): Bristol-Myers Squibb Company, USA  
SOURCE: PCT Int. Appl., 81 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004012663	A2	20040212	WO 2003-US23989	20030731
WO 2004012663	A3	20040708		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,				

LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM,  
 PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN,  
 TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW  
 RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,  
 KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,  
 FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,  
 BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2004063698 A1 20040401 US 2003-632197 20030731

PRIORITY APPLN. INFO.: MARPAT 140:177322 US 2002-400237P P 20020801

OTHER SOURCE(S): MARPAT 140:177322

ED Entered STN: 13 Feb 2004

AB MMP or TACE-inhibiting hydroxamic acid derivs. for use in treatment of diseases are disclosed. Thus, 3,N-dihydroxy-2,2-dimethyl-3-[6-(2-methylquinolin-4-ylmethoxy)naphthalen-2-yl]propionamide (I), 4,N-dihydroxy-4-[4-(2-methylquinolin-4-ylmethoxy)phenyl]butyramide (II), N-Hydroxy-2-{2-[4-(2-methylquinolin-4-ylmethoxy)phenyl]tetrahydrofuran-2-yl}acetamide (III), and 3,N-dihydroxy-3-(6-methoxynaphthalen-2-yl)-2,2-dimethylpropionamide (IV) as well as 23 other compds. were synthesized and tested as MMP inhibitors. Some of these compds. inhibited MMPs with Ki's ≤ 10 μM.

IC ICM A61K

CC 7-3 (Enzymes)

Section cross-reference(s): 1

ST hydroxamic acid deriv matrix metalloproteinases inhibitor pharmaceutical; tumor necrosis factor converting enzyme inhibitor hydroxamic acid deriv

IT Inflammation

(Crohn's disease; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNFα converting enzyme for use in treatment of diseases)

IT Intestine, disease

(Crohn's; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNFα converting enzyme for use in treatment of diseases)

IT Arthritis

(Felty's syndrome; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNFα converting enzyme for use in treatment of diseases)

IT Arthritis

(Reiter's syndrome; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNFα converting enzyme for use in treatment of diseases)

IT Granulomatous disease

(Wegener's granulomatosis; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNFα converting enzyme for use in treatment of diseases)

IT Inflammation

Reproductive tract, disease

(adnexitis; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNFα converting enzyme for use in treatment of diseases)

IT Liver, disease

(alc.-induced; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNFα converting enzyme for use in treatment of diseases)

IT Lung

(alveolus, hyperoxic injury to; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNFα converting enzyme for use in treatment of diseases)

IT Antiarteriosclerotics

(antiatherosclerotics; hydroxamic acid derivative inhibitors of matrix

metalloproteinases and/or TNF $\alpha$  converting enzyme for use in treatment of diseases)

IT Disease, animal  
(arthropathy, hydrarthrosis; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNF $\alpha$  converting enzyme for use in treatment of diseases)

IT Disease, animal  
(arthropathy; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNF $\alpha$  converting enzyme for use in treatment of diseases)

IT Disease, animal  
(asthenia, post-radiation; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNF $\alpha$  converting enzyme for use in treatment of diseases)

IT Dermatitis  
(atopic; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNF $\alpha$  converting enzyme for use in treatment of diseases)

IT Hepatitis  
(autoimmune; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNF $\alpha$  converting enzyme for use in treatment of diseases)

IT Fatigue, biological  
(chronic fatigue syndrome; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNF $\alpha$  converting enzyme for use in treatment of diseases)

IT Lung, disease  
(chronic obstructive; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNF $\alpha$  converting enzyme for use in treatment of diseases)

IT Eye, disease  
(cornea, ulcer; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNF $\alpha$  converting enzyme for use in treatment of diseases)

IT Ulcer  
(corneal; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNF $\alpha$  converting enzyme for use in treatment of diseases)

IT Ulcer  
(cutaneous, pyoderma gangrenosum; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNF $\alpha$  converting enzyme for use in treatment of diseases)

IT Joint, anatomical  
(disease, hydrarthrosis; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNF $\alpha$  converting enzyme for use in treatment of diseases)

IT Joint, anatomical  
(disease; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNF $\alpha$  converting enzyme for use in treatment of diseases)

IT Blood coagulation  
(disorder; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNF $\alpha$  converting enzyme for use in treatment of diseases)

IT Heart, disease  
(failure; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNF $\alpha$  converting enzyme for use in treatment of diseases)

IT Muscle, disease  
(fibromyalgia; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNF $\alpha$  converting enzyme for use in

treatment of diseases)

IT Gingiva, disease  
Inflammation  
(gingivitis; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNF $\alpha$  converting enzyme for use in treatment of diseases)

IT Transplant and Transplantation  
(graft-vs.-host reaction; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNF $\alpha$  converting enzyme for use in treatment of diseases)

IT Acute-phase response  
Allergy  
Allergy inhibitors  
Aneurysm  
Anorexia  
Anti-AIDS agents  
Anti-infective agents  
Antiarthritis  
Antiasthmatics  
Antibacterial agents  
Antirheumatic agents  
Antitumor agents  
Asthma  
Atherosclerosis  
Autoimmune disease  
Behcet's syndrome  
Cachexia  
Cardiovascular system, disease  
Dermatitis  
Dermatomyositis  
Emphysema  
Fever and Hyperthermia  
Fibrosis  
Gout  
Hemorrhage  
Human  
Infection  
Inflammation  
Lyme disease  
Meningitis  
Multiple sclerosis  
Myasthenia gravis  
Neoplasm  
Osteoarthritis  
Psoriasis  
Rheumatic fever  
Rheumatoid arthritis  
Sarcoidosis  
Sepsis  
Shock (circulatory collapse)  
Sjogren's syndrome  
(hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNF $\alpha$  converting enzyme for use in treatment of diseases)

IT Human immunodeficiency virus  
Mycobacterium  
(infection with; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNF $\alpha$  converting enzyme for use in treatment of diseases)

IT Arthritis  
(infectious; hydroxamic acid derivative inhibitors of matrix

metalloproteinases and/or TNF $\alpha$  converting enzyme for use in treatment of diseases)

IT Reperfusion  
(injury, post-ischemic; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNF $\alpha$  converting enzyme for use in treatment of diseases)

IT Rheumatoid arthritis  
(juvenile; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNF $\alpha$  converting enzyme for use in treatment of diseases)

IT Eye, disease  
(macula, degeneration, age-related; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNF $\alpha$  converting enzyme for use in treatment of diseases)

IT Glaucoma (disease)  
(neovascular; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNF $\alpha$  converting enzyme for use in treatment of diseases)

IT Inflammation  
Periodontium, disease  
(periodontitis; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNF $\alpha$  converting enzyme for use in treatment of diseases)

IT Bone, disease  
Inflammation  
(polychondritis, relapsing; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNF $\alpha$  converting enzyme for use in treatment of diseases)

IT Myositis  
(polymyositis; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNF $\alpha$  converting enzyme for use in treatment of diseases)

IT Arthritis  
(psoriatic arthritis; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNF $\alpha$  converting enzyme for use in treatment of diseases)

IT Injury  
(reperfusion, post-ischemic; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNF $\alpha$  converting enzyme for use in treatment of diseases)

IT Connective tissue, disease  
(scleroderma; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNF $\alpha$  converting enzyme for use in treatment of diseases)

IT Inflammation  
Spinal column, disease  
(spondylitis; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNF $\alpha$  converting enzyme for use in treatment of diseases)

IT Brain, disease  
(stroke; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNF $\alpha$  converting enzyme for use in treatment of diseases)

IT Lupus erythematosus  
(systemic; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNF $\alpha$  converting enzyme for use in treatment of diseases)

IT Skin, disease  
(ulcer, pyoderma gangrenosum; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNF $\alpha$  converting enzyme for use in treatment of diseases)

IT Inflammation  
 Intestine, disease  
 (ulcerative colitis; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNF $\alpha$  converting enzyme for use in treatment of diseases)

IT Eye, disease  
 Inflammation  
 (uveitis; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNF $\alpha$  converting enzyme for use in treatment of diseases)

IT Blood vessel, disease  
 Inflammation  
 (vasculitis; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNF $\alpha$  converting enzyme for use in treatment of diseases)

IT Glucocorticoids  
 RL: BSU (Biological study, unclassified); BIOL (Biological study)  
 (withdrawal syndrome; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNF $\alpha$  converting enzyme for use in treatment of diseases)

IT 17031-92-4, Calcium pyrophosphate dihydrate  
 RL: BSU (Biological study, unclassified); BIOL (Biological study)  
 (deposition, disease; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNF $\alpha$  converting enzyme for use in treatment of diseases)

IT 141907-41-7, Matrix metalloproteinase  $\alpha$ -converting enzyme 151769-16-3, Tumor necrosis factor  
 RL: BSU (Biological study, unclassified); BIOL (Biological study)  
 (hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNF $\alpha$  converting enzyme for use in treatment of diseases)

IT 96-32-2, Methyl bromoacetate 99-93-4, 1-(4-Hydroxyphenyl)ethanone  
 100-39-0, Benzyl bromide 103-25-3, 3-Phenylpropionic acid methyl ester  
 106-41-2, 4-Bromophenol 123-08-0, 4-Hydroxybenzaldehyde 141-78-6,  
 Ethyl acetate, reactions 554-12-1, Methyl propionate 594-19-4,  
 tert-Butyl lithium 598-30-1, sec-Butyl lithium 623-47-2, Ethyl  
 propiolate 886-51-1 1619-62-1, Diethyl dimethylmalonate 2412-80-8,  
 4-Methylpentanoic acid methyl ester 5111-65-9, 2-Bromo-6-  
 methoxynaphthalene 7150-55-2, 4-Chloro-1-(4-hydroxyphenyl)butan-1-one  
 15231-91-1, 6-Bromonaphthalen-2-ol 15823-04-8 18162-48-6 28819-26-3  
 33611-43-7 37493-31-5 57906-98-6 84199-98-4 90610-07-4  
 119740-95-3 155339-52-9 156002-64-1, (Tetrahydropyran-4-yl)acetic acid  
 methyl ester 162504-75-8 288399-19-9, 4-Chloromethyl-2-methylquinoline  
 656803-41-7 656803-51-9  
 RL: RCT (Reactant); RACT (Reactant or reagent)  
 (hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNF $\alpha$  converting enzyme for use in treatment of diseases)

IT 4397-53-9P, 4-Benzoyloxybenzaldehyde 6793-92-6P, 1-Bromo-4-  
 benzoyloxybenzene 100751-65-3P 656802-94-7P 656802-95-8P  
 656802-96-9P 656802-97-0P 656802-98-1P 656802-99-2P 656803-00-8P  
 656803-01-9P 656803-02-0P 656803-03-1P 656803-04-2P 656803-38-2P  
 656803-40-6P  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT  
 (Reactant or reagent)  
 (hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNF $\alpha$  converting enzyme for use in treatment of diseases)

IT 656802-67-4P 656802-68-5P 656802-69-6P  
 656802-70-9P 656802-71-0P 656802-72-1P  
 656802-73-2P 656802-74-3P 656802-75-4P  
 656802-76-5P 656802-77-6P 656802-78-7P  
 656802-79-8P 656802-80-1P 656802-81-2P

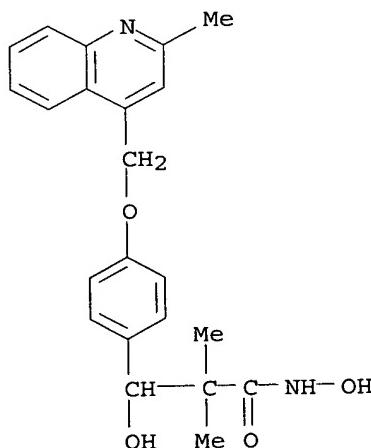
656802-82-3P 656802-83-4P 656802-84-5P  
 656802-85-6P 656802-86-7P 656802-87-8P  
 656802-88-9P 656802-89-0P 656802-90-3P  
 656802-91-4P 656802-92-5P 656802-93-6P  
 656803-05-3P 656803-06-4P 656803-07-5P  
 656803-08-6P 656803-09-7P 656803-11-1P  
 656803-12-2P 656803-14-4P 656803-16-6P  
 656803-18-8P 656803-20-2P 656803-22-4P  
 656803-24-6P 656803-26-8P 656803-28-0P  
 656803-30-4P 656803-32-6P 656803-33-7P  
 656803-35-9P 656803-36-0P

RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNF $\alpha$  converting enzyme for use in treatment of diseases)

IT 656802-67-4P 656802-68-5P 656802-69-6P  
 656802-70-9P 656802-71-0P 656802-72-1P  
 656802-73-2P 656802-74-3P 656802-75-4P  
 656802-76-5P 656802-77-6P 656802-78-7P  
 656802-79-8P 656802-80-1P 656802-81-2P  
 656802-82-3P 656802-83-4P 656802-84-5P  
 656802-85-6P 656802-86-7P 656802-87-8P  
 656802-88-9P 656802-89-0P 656802-90-3P  
 656802-91-4P 656802-92-5P 656803-05-3P  
 656803-06-4P 656803-07-5P 656803-08-6P  
 656803-09-7P 656803-11-1P 656803-12-2P  
 656803-14-4P 656803-16-6P 656803-18-8P  
 656803-20-2P 656803-22-4P 656803-24-6P  
 656803-26-8P 656803-28-0P 656803-30-4P  
 656803-32-6P 656803-33-7P 656803-35-9P  
 656803-36-0P

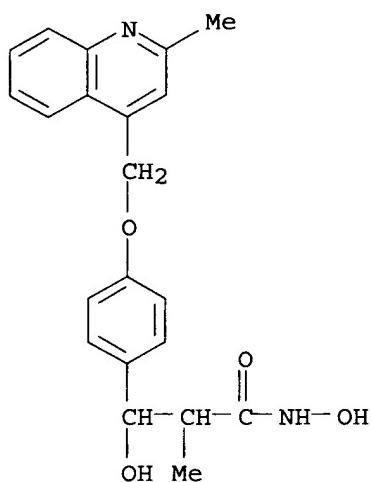
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNF $\alpha$  converting enzyme for use in treatment of diseases)

RN 656802-67-4 HCAPLUS  
 CN Benzenepropanamide, N, $\beta$ -dihydroxy- $\alpha$ , $\alpha$ -dimethyl-4-[(2-methyl-4-quinolinyl)methoxy]- (9CI) (CA INDEX NAME)



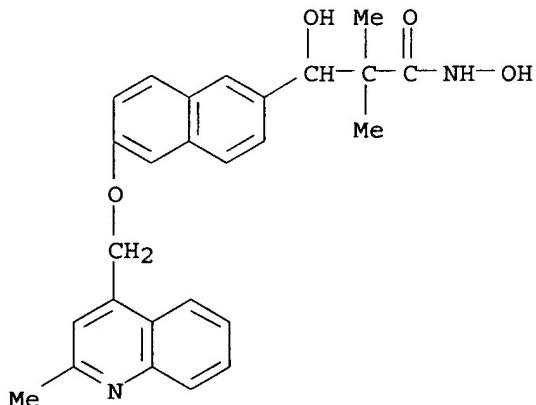
RN 656802-68-5 HCAPLUS

CN Benzenepropanamide, N, $\beta$ -dihydroxy- $\alpha$ -methyl-4-[(2-methyl-4-quinolinyl)methoxy]- (9CI) (CA INDEX NAME)



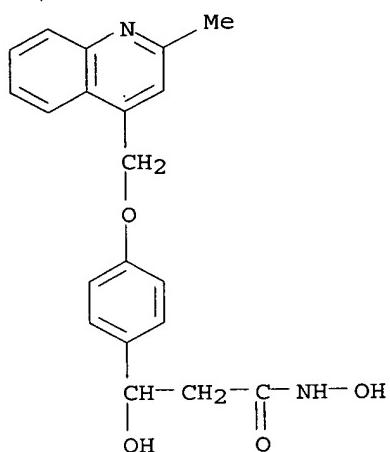
RN 656802-69-6 HCAPLUS

CN 2-Naphthalenepropanamide, N, $\beta$ -dihydroxy- $\alpha$ , $\alpha$ -dimethyl-6-[(2-methyl-4-quinolinyl)methoxy]- (9CI) (CA INDEX NAME)



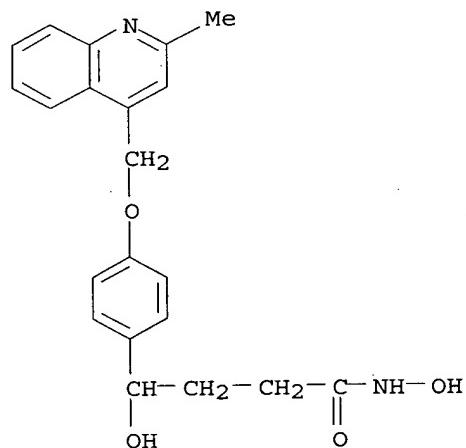
RN 656802-70-9 HCAPLUS

CN Benzenepropanamide, N, $\beta$ -dihydroxy-4-[(2-methyl-4-quinolinyl)methoxy]- (9CI) (CA INDEX NAME)



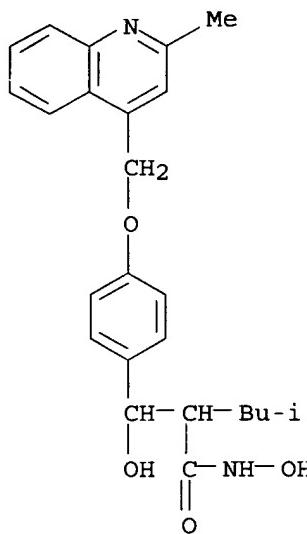
RN 656802-71-0 HCAPLUS

CN Benzenebutanamide, N,γ-dihydroxy-4-[(2-methyl-4-quinoliny) methoxy] -  
(9CI) (CA INDEX NAME)



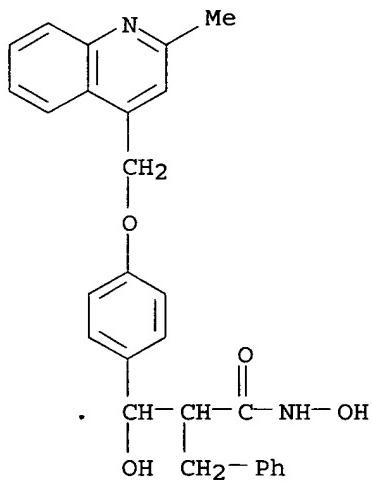
RN 656802-72-1 HCAPLUS

CN Benzenepropanamide, N,β-dihydroxy-α-(2-methylpropyl)-4-[(2-methyl-4-quinoliny) methoxy] - (9CI) (CA INDEX NAME)



RN 656802-73-2 HCAPLUS

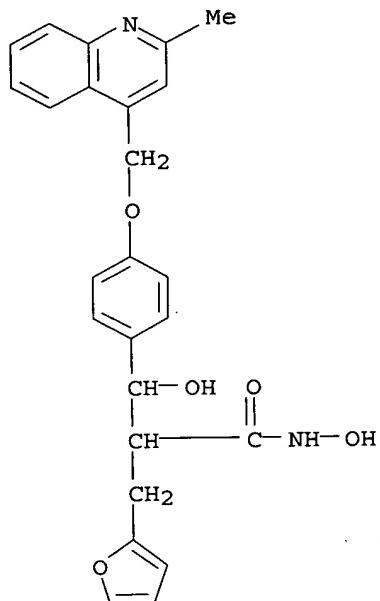
CN Benzenepropanamide, N,β-dihydroxy-4-[(2-methyl-4-quinolinyl)methoxy]-α-(phenylmethyl)- (9CI) (CA INDEX NAME)



RN 656802-74-3 HCAPLUS

CN 2-Furanpropanamide, N-hydroxy-α-[hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]- (9CI) (CA INDEX NAME)

PAGE 1-A

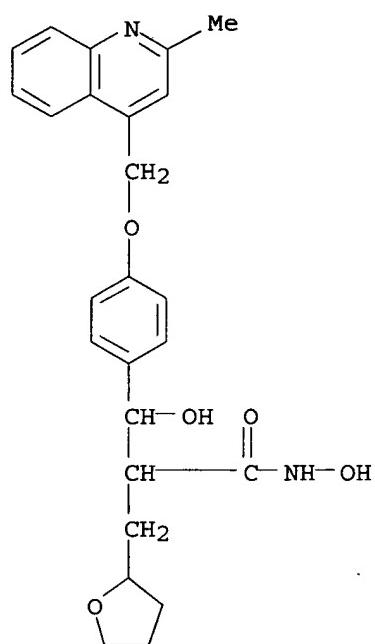


PAGE 2-A

RN 656802-75-4 HCAPLUS

CN 2-Furanpropanamide, tetrahydro-N-hydroxy-alpha-[hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]- (9CI) (CA INDEX NAME)

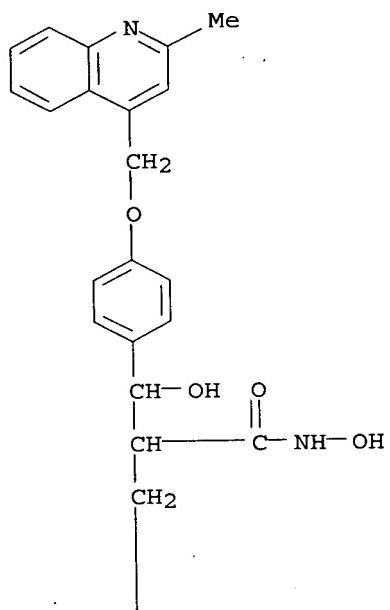
PAGE 1-A



PAGE 2-A

RN 656802-76-5 HCPLUS  
CN Benzenepropanamide, N,β-dihydroxy-α-[(4-methoxyphenyl)methyl]-4-  
[(2-methyl-4-quinolinyl)methoxy]- (9CI) (CA INDEX NAME)

PAGE 1-A



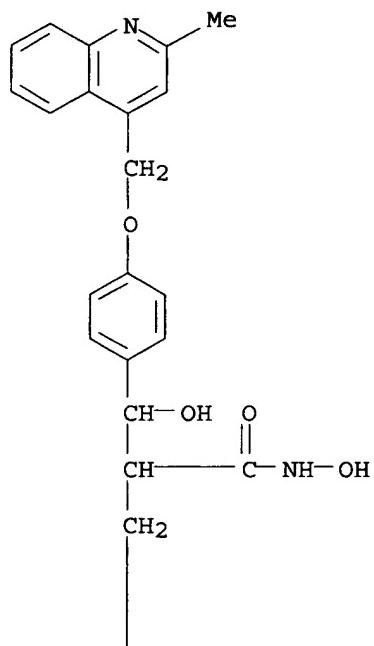
PAGE 2-A



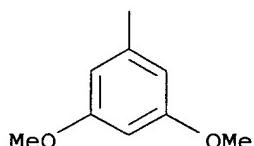
RN 656802-77-6 HCAPLUS

CN Benzenepropanamide, N-hydroxy- $\alpha$ -[hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-3,5-dimethoxy- (9CI) (CA INDEX NAME)

PAGE 1-A

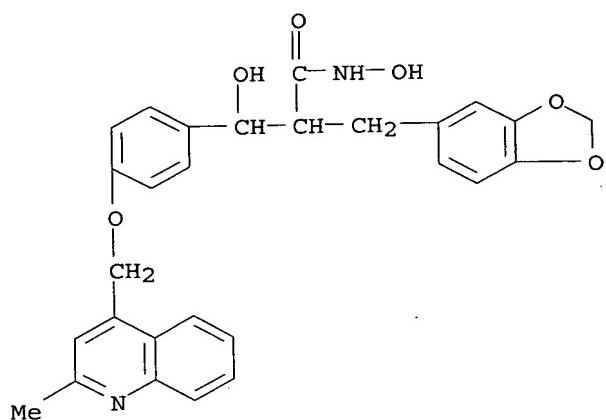


PAGE 2-A



RN 656802-78-7 HCAPLUS

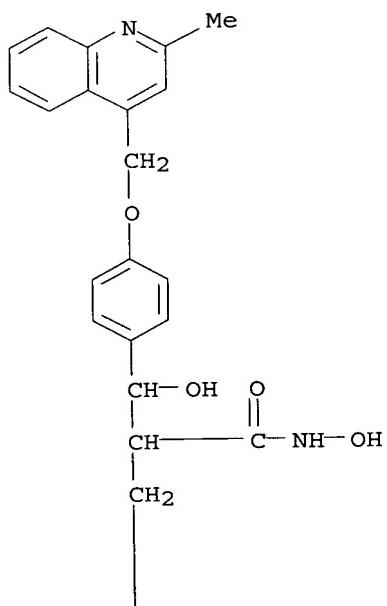
CN 1,3-Benzodioxole-5-propanamide, N-hydroxy-alpha-[hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]- (9CI) (CA INDEX NAME)



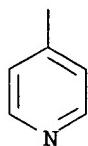
RN 656802-79-8 HCAPLUS

CN 4-Pyridinepropanamide, N-hydroxy- $\alpha$ - [hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]- (9CI) (CA INDEX NAME)

PAGE 1-A



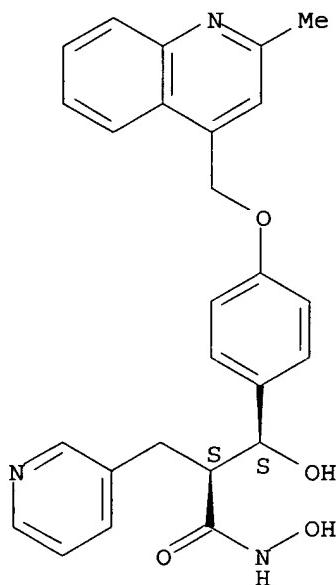
PAGE 2-A



RN 656802-80-1 HCPLUS

CN 3-Pyridinepropanamide, N-hydroxy- $\alpha$ -[(R)-hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-, ( $\alpha$ R)-rel- (9CI) (CA INDEX NAME)

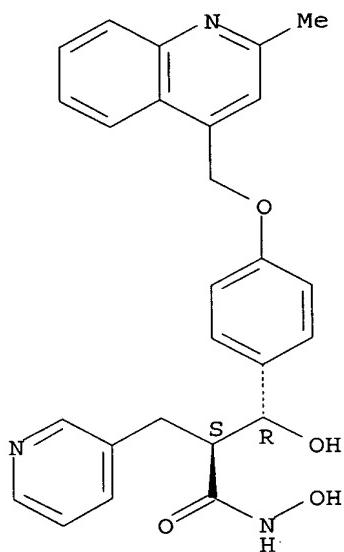
Relative stereochemistry.



RN 656802-81-2 HCPLUS

CN 3-Pyridinepropanamide, N-hydroxy- $\alpha$ -[(R)-hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-, ( $\alpha$ S)-rel- (9CI) (CA INDEX NAME)

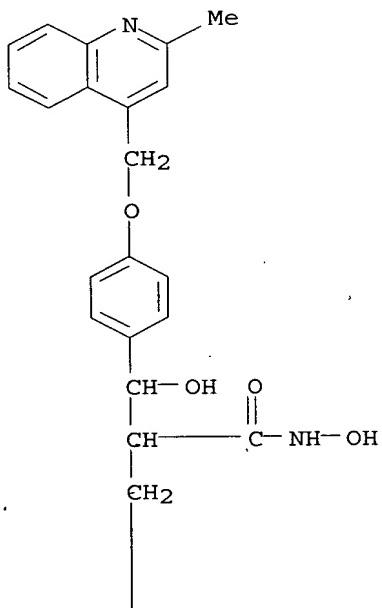
Relative stereochemistry.



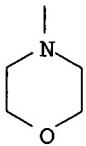
RN 656802-82-3 HCPLUS

CN 4-Morpholinepropanamide, N-hydroxy- $\alpha$ -[hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]- (9CI) (CA INDEX NAME)

PAGE 1-A



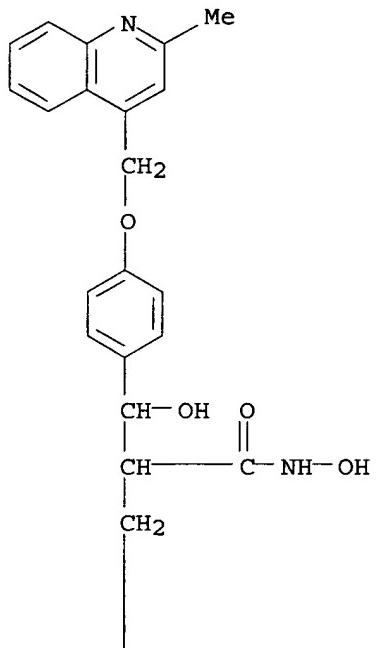
PAGE 2-A



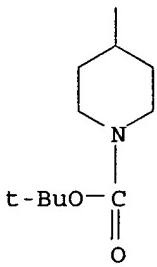
RN 656802-83-4 HCAPLUS

CN 1-Piperidinecarboxylic acid, 4-[3-(hydroxyamino)-2-[hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-3-oxopropyl]-, 1,1-dimethylethyl ester  
(9CI) (CA INDEX NAME)

PAGE 1-A



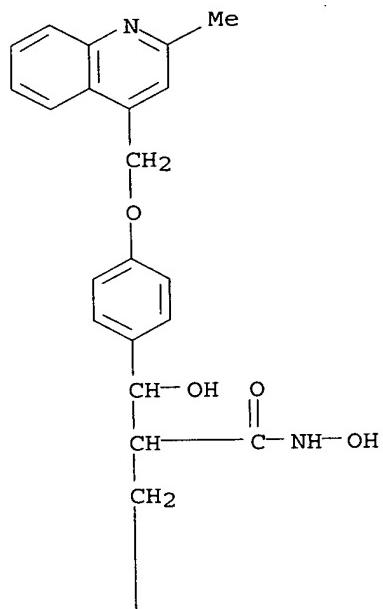
PAGE 2-A



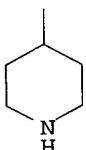
RN 656802-84-5 HCAPLUS

CN 4-Piperidinepropanamide, N-hydroxy- $\alpha$ -[hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]- (9CI) (CA INDEX NAME)

PAGE 1-A

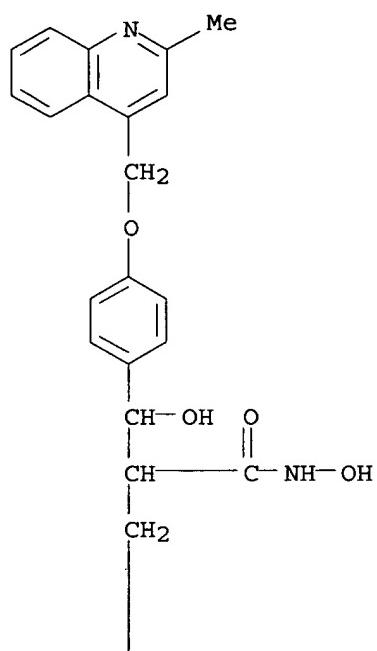


PAGE 2-A

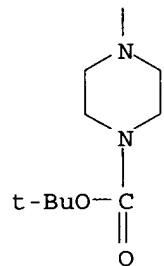


RN 656802-85-6 HCAPLUS  
CN 1-Piperazinecarboxylic acid, 4-[3-(hydroxyamino)-2-[hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-3-oxopropyl]-, 1,1-dimethylethyl ester  
(9CI) (CA INDEX NAME)

PAGE 1-A



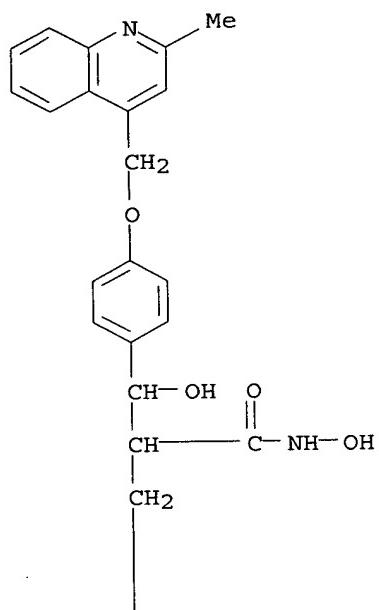
PAGE 2-A



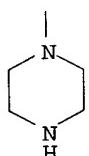
RN 656802-86-7 HCPLUS

CN 1-Piperazinepropanamide, N-hydroxy- $\alpha$ -[hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]- (9CI) (CA INDEX NAME)

PAGE 1-A

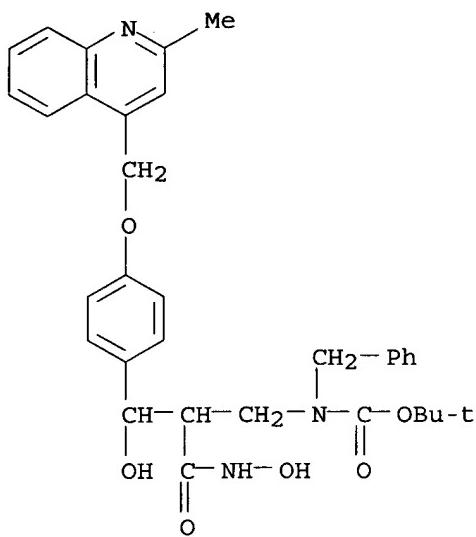


PAGE 2-A



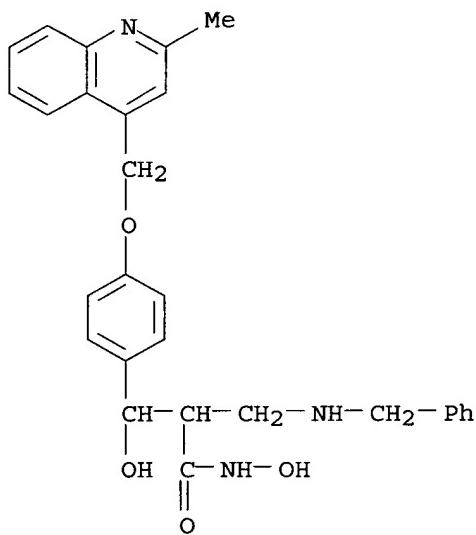
RN 656802-87-8 HCPLUS

CN Carbamic acid, [3-(hydroxyamino)-2-[hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-3-oxopropyl](phenylmethyl)-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



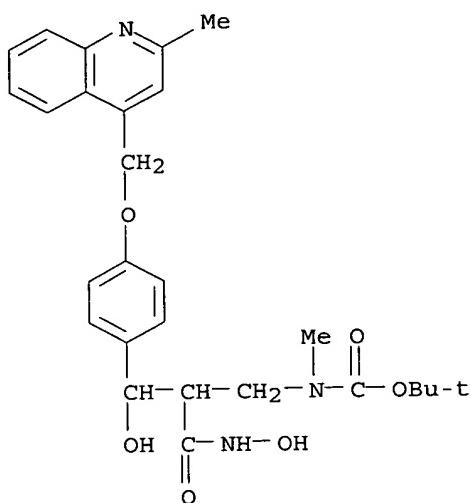
RN 656802-88-9 HCPLUS

CN Benzenepropanamide, N,β-dihydroxy-4-[(2-methyl-4-quinolinyl)methoxy]-  
α-[(phenylmethyl)amino]methyl- (9CI) (CA INDEX NAME)



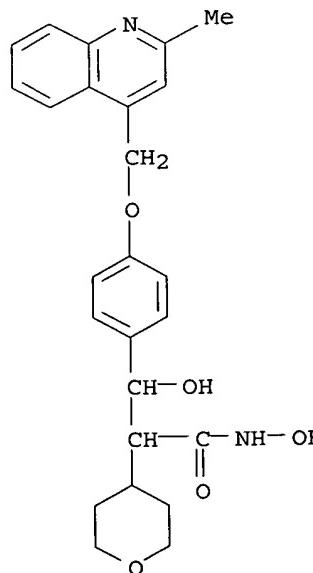
RN 656802-89-0 HCPLUS

CN Carbamic acid, [3-(hydroxyamino)-2-[hydroxy[4-[(2-methyl-4-  
quinolinyl)methoxy]phenyl]methyl]-3-oxopropyl]methyl-, 1,1-dimethylethyl  
ester (9CI) (CA INDEX NAME)



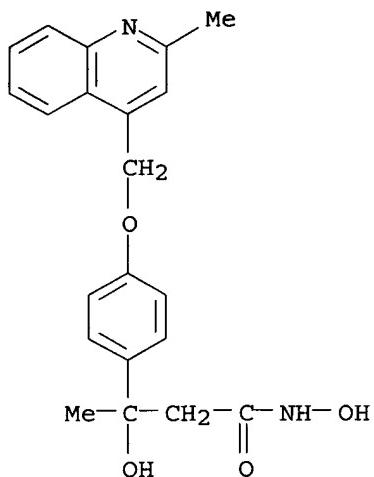
RN 656802-90-3 HCAPLUS

CN 2H-Pyran-4-acetamide, tetrahydro-N-hydroxy-alpha-[hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]- (9CI) (CA INDEX NAME)



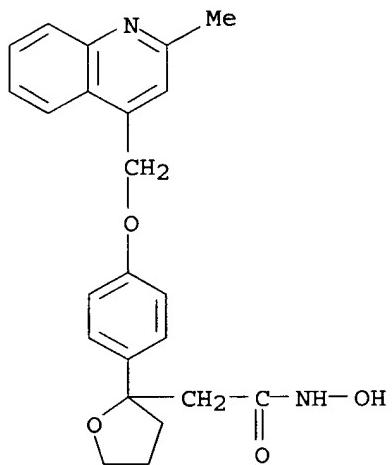
RN 656802-91-4 HCAPLUS

CN Benzenepropanamide, N,b-dihydroxy-beta-methyl-4-[(2-methyl-4-quinolinyl)methoxy]- (9CI) (CA INDEX NAME)



RN 656802-92-5 HCAPLUS

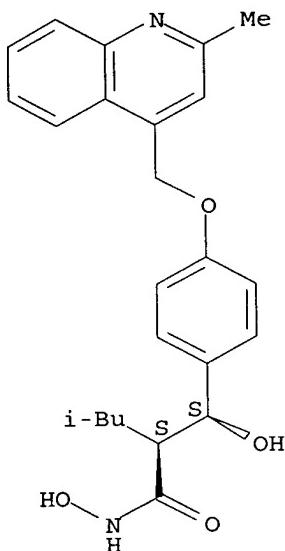
CN 2-Furanacetamide, tetrahydro-N-hydroxy-2-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]- (9CI) (CA INDEX NAME)



RN 656803-05-3 HCAPLUS

CN Benzenepropanamide, N,β-dihydroxy-α-(2-methylpropyl)-4-[(2-methyl-4-quinolinyl)methoxy]-, (αR,βR)-rel- (9CI) (CA INDEX NAME)

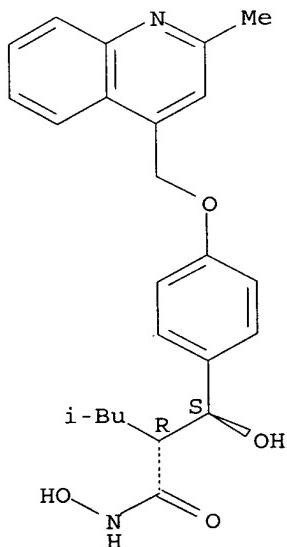
Relative stereochemistry.



RN 656803-06-4 HCAPLUS

CN Benzene propanamide, N,β-dihydroxy-α-(2-methylpropyl)-4-[(2-methyl-4-quinolinyl)methoxy]-, (αR,βS)-rel- (9CI) (CA INDEX NAME)

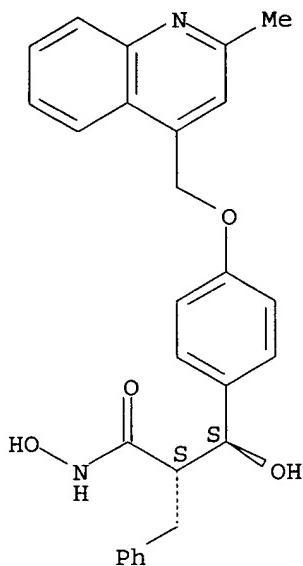
Relative stereochemistry.



RN 656803-07-5 HCAPLUS

CN Benzene propanamide, N,β-dihydroxy-4-[(2-methyl-4-quinolinyl)methoxy]-α-(phenylmethyl)-, (αR,βR)-rel- (9CI) (CA INDEX NAME)

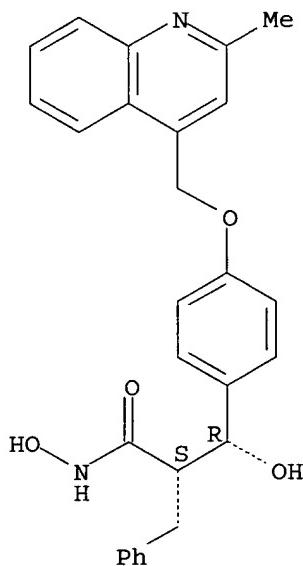
Relative stereochemistry.



RN 656803-08-6 HCPLUS

CN Benzenepropanamide, N,β-dihydroxy-4-[(2-methyl-4-quinolinyl)methoxy]-α-(phenylmethyl)-, (αR,βS)-rel- (9CI) (CA INDEX NAME)

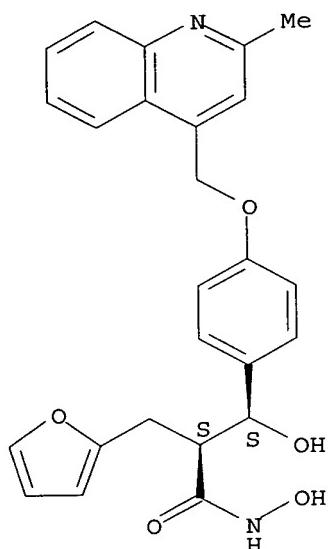
Relative stereochemistry.



RN 656803-09-7 HCPLUS

CN 2-Furanpropanamide, N-hydroxy-α-[(R)-hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-, (αR)-rel- (9CI) (CA INDEX NAME)

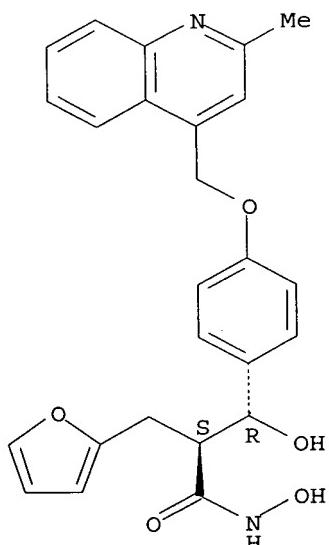
Relative stereochemistry.



RN 656803-11-1 HCPLUS

CN 2-Furanpropanamide, N-hydroxy- $\alpha$ -[(R)-hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-, ( $\alpha$ S)-rel- (9CI) (CA INDEX NAME)

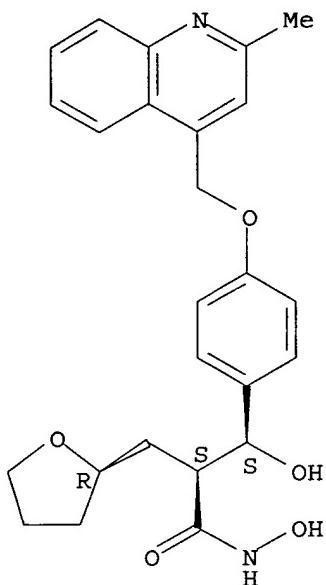
Relative stereochemistry.



RN 656803-12-2 HCPLUS

CN 2-Furanpropanamide, tetrahydro-N-hydroxy- $\alpha$ -[(R)-hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-, ( $\alpha$ R,2S)-rel- (9CI) (CA INDEX NAME)

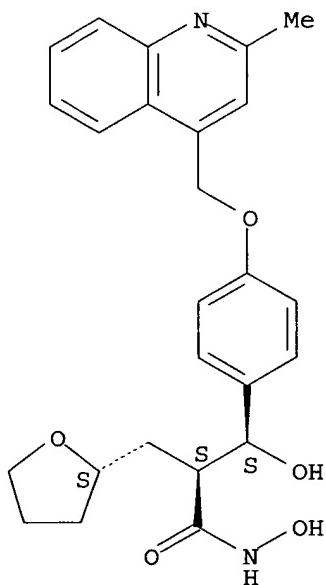
Relative stereochemistry.



RN 656803-14-4 HCPLUS

CN 2-Furanpropanamide, tetrahydro-N-hydroxy-alpha-[ (R) -hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-, (alpha R, 2R)-rel- (9CI) (CA INDEX NAME)

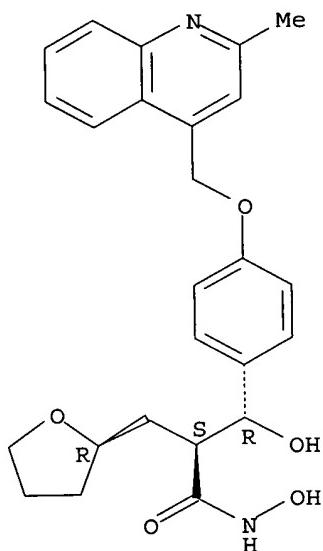
Relative stereochemistry.



RN 656803-16-6 HCPLUS

CN 2-Furanpropanamide, tetrahydro-N-hydroxy-alpha-[ (R) -hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-, (alpha S, 2R)-rel- (9CI) (CA INDEX NAME)

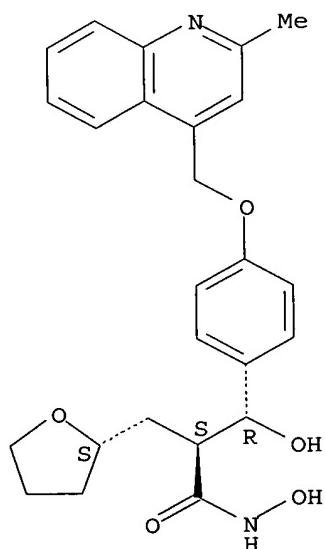
Relative stereochemistry.



RN 656803-18-8 HCPLUS

CN 2-Furanpropanamide, tetrahydro-N-hydroxy-alpha-[(R)-hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-, (alphaS,2S)-rel- (9CI) (CA INDEX NAME)

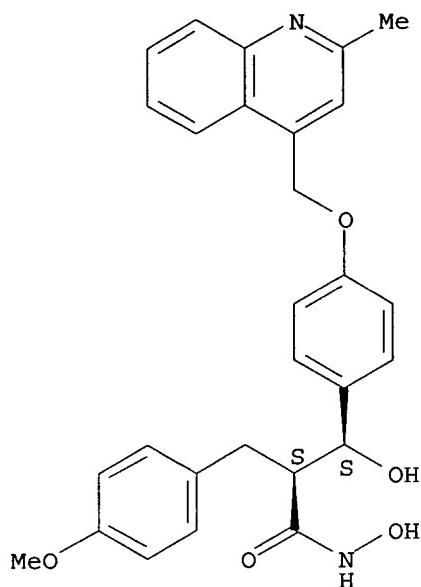
Relative stereochemistry.



RN 656803-20-2 HCPLUS

CN Benzene propanamide, N,beta-dihydroxy-alpha-[(4-methoxyphenyl)methyl]-4-[(2-methyl-4-quinolinyl)methoxy]-, (alphaR,betaR)-rel- (9CI) (CA INDEX NAME)

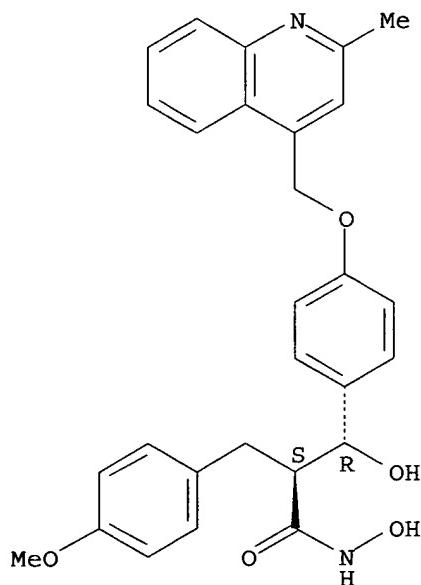
Relative stereochemistry.



RN 656803-22-4 HCAPLUS

CN Benzenepropanamide, N,β-dihydroxy- $\alpha$ -[(4-methoxyphenyl)methyl]-4-[(2-methyl-4-quinolinyl)methoxy]-, ( $\alpha$ R, $\beta$ S)-rel- (9CI) (CA INDEX NAME)

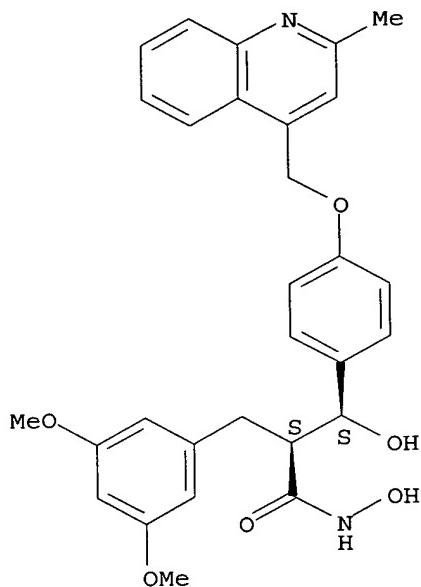
Relative stereochemistry.



RN 656803-24-6 HCAPLUS

CN Benzenepropanamide, N-hydroxy- $\alpha$ -[(R)-hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-3,5-dimethoxy-, ( $\alpha$ R)-rel- (9CI) (CA INDEX NAME)

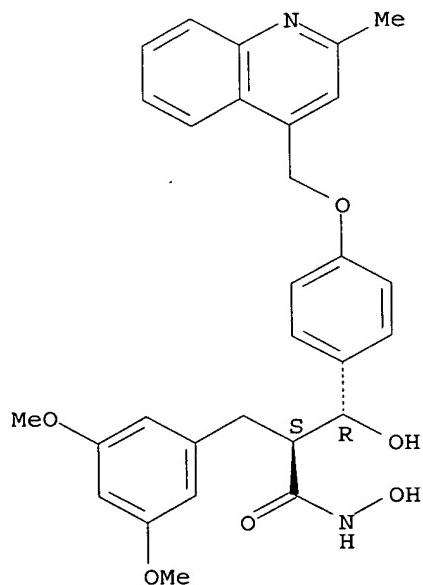
Relative stereochemistry.



RN 656803-26-8 HCPLUS

CN Benzenepropanamide, N-hydroxy- $\alpha$ -[(R)-hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-, ( $\alpha$ S)-rel- (9CI)  
(CA INDEX NAME)

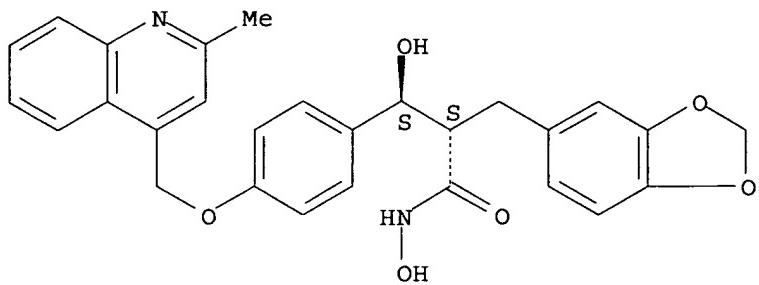
Relative stereochemistry.



RN 656803-28-0 HCPLUS

CN 1,3-Benzodioxole-5-propanamide, N-hydroxy- $\alpha$ -[(R)-hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-, ( $\alpha$ R)-rel- (9CI) (CA INDEX NAME)

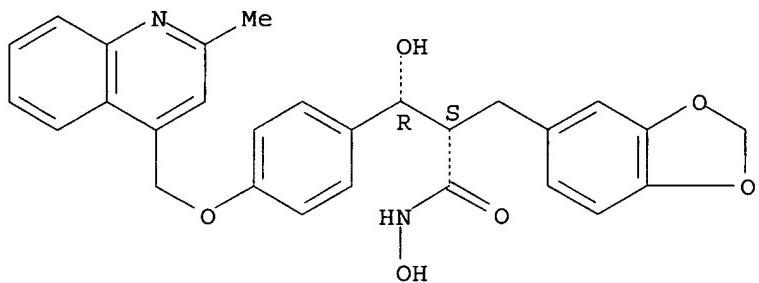
Relative stereochemistry.



RN 656803-30-4 HCAPLUS

CN 1,3-Benzodioxole-5-propanamide, N-hydroxy- $\alpha$ -[ (R)-hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-, ( $\alpha$ S)-rel- (9CI) (CA INDEX NAME)

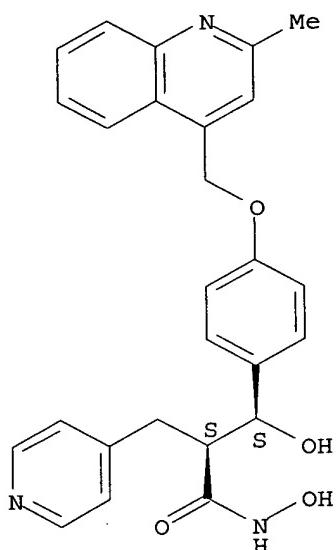
Relative stereochemistry.



RN 656803-32-6 HCAPLUS

CN 4-Pyridinepropanamide, N-hydroxy- $\alpha$ -[ (R)-hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-, ( $\alpha$ R)-rel- (9CI) (CA INDEX NAME)

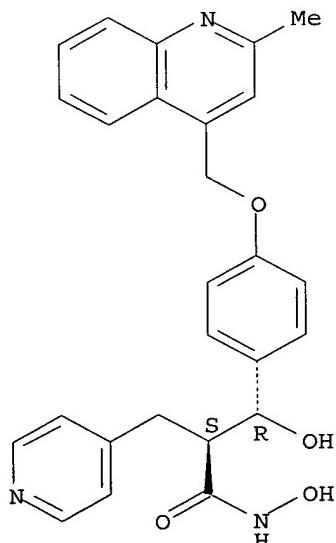
Relative stereochemistry.



RN 656803-33-7 HCAPLUS

CN 4-Pyridinepropanamide, N-hydroxy- $\alpha$ -[(R)-hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-, ( $\alpha$ S)-rel- (9CI) (CA INDEX NAME)

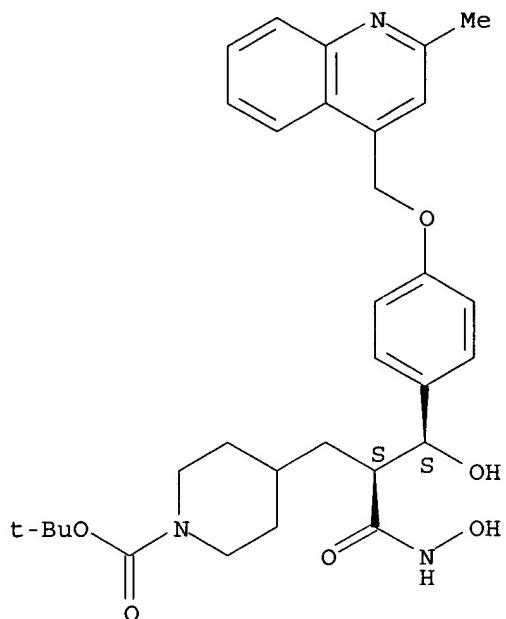
Relative stereochemistry.



RN 656803-35-9 HCAPLUS

CN 1-Piperidinecarboxylic acid, 4-[(2R)-3-(hydroxyamino)-2-[(R)-hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-3-oxopropyl]-, 1,1-dimethylethyl ester, rel- (9CI) (CA INDEX NAME)

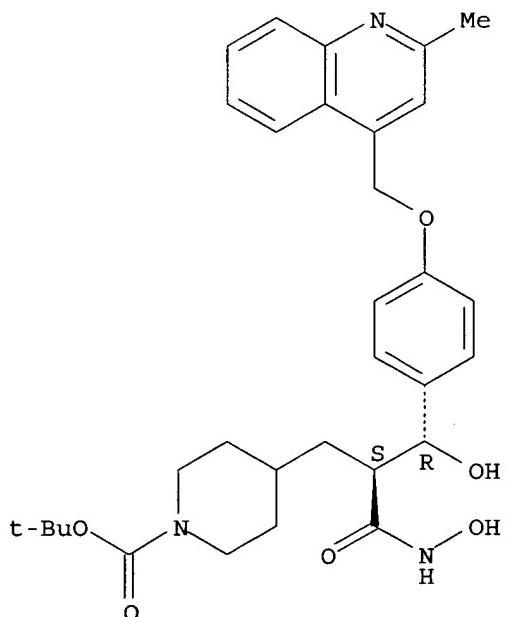
Relative stereochemistry.



RN 656803-36-0 HCAPLUS

CN 1-Piperidinecarboxylic acid, 4-[(2R)-3-(hydroxyamino)-2-[(S)-hydroxy[4-[(2-methyl-4-quinolinyl)methoxyl]phenyl]methyl]-3-oxopropyl]-, 1,1-dimethylethyl ester, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



L66 ANSWER 2 OF 26 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 6

ACCESSION NUMBER: 1995:931621 HCAPLUS

DOCUMENT NUMBER: 124:146141

TITLE: N-Hydroxy-N-[4-(2-phenyloxazolyl-

-thiazolylmethoxy)benzyl]ureas as 5-lipoxygenase inhibitors and inhibitors of oxidative modification of low density lipoprotein

INVENTOR(S): Malamas, Michael S.; Nelson, James A.  
 PATENT ASSIGNEE(S): American Home Products Corp., USA  
 SOURCE: U.S., 15 pp.  
 CODEN: USXXAM  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5459154	A	19951017	US 1993-148603	19931108
US 5504097	A	19960402	US 1995-423061	19950417
			US 1993-148603	A3 19931108

## PRIORITY APPLN. INFO.:

OTHER SOURCE(S): MARPAT 124:146141

ED Entered STN: 21 Nov 1995

AB This invention relates to compds. having 5-lipoxygenase inhibiting properties and inhibition of oxidative modification of low d. lipoprotein which have the formula I wherein: R1 and R3 are independently hydrogen, halogen, C1-C6 alkyl, C1-C6 alkoxy, trifluoromethyl, or C1-C6 trifluoroalkoxy; R2 is hydrogen or methyl; R4 is hydrogen, Me or hydroxy; R5 is hydrogen, NH<sub>2</sub>, C1-C6 alkyl, C6-C10 aryl, C6-C10 aryl-C1-C6 alkylene, or N:Me<sub>2</sub>; X and Y are independently O or S; and n is 0 or 1; or a pharmaceutically acceptable salt thereof. Compds. which inhibit 5-lipoxygenase are useful in the treatment of diseases mediated by leukotrienes such as inflammation or bronchoconstriction. Compds. which inhibit oxidative metabolism of low d. lipoprotein are useful in the inhibition of atherosclerotic plaque formation. Thus, e.g., carbamoylation of N-[4-(5-methyl-2-phenyl-oxazol-4-ylmethoxy)benzyl]hydroxylamine (preparation given) with trimethylsilyl isocyanate afforded 1-hydroxy-1-[4-(5-methyl-2-phenyloxazol-4-ylmethoxy)benzyl]urea (I; R1 = R3 = R4 = R5 = H, R2 = Me, n = 0, Y = O) which exhibited 69% inhibition of LTB4 synthesis at 25 mg/kg p.o. in the reverse passive Arthus pleurisy assay in rats, 38% inhibition of bronchoconstriction (at 10 mg/kg i.v.) in guinea pigs induced by exogenous antigen, and inhibition of copper ion mediated oxidation of low d. lipoprotein with IC<sub>50</sub> = 1.1 μM.

IC ICM C07D263-32  
 ICS C07D277-30; A61K031-425; A61K031-42

INCL 514374000

CC 28-7 (Heterocyclic Compounds (More Than One Hetero Atom))  
 Section cross-reference(s): 1, 63

ST hydroxyurea phenyloxazolylmethoxybenzyl phenylthiazolylmethoxybenzyl lipoxygenase inhibitor; oxazolylmethoxybenzylhydroxyurea lipoxygenase inhibitor; thiazolylmethoxybenzylhydroxyurea lipoxygenase inhibitor; low density lipoprotein antioxidant oxazolylmethoxybenzylhydroxyurea thiazolylmethoxybenzylhydroxyurea; bronchodilator oxazolylmethoxybenzylhydroxyurea thiazolylmethoxybenzylhydroxyurea; antiinflammatory oxazolylmethoxybenzylhydroxyurea thiazolylmethoxybenzylhydroxyurea; antiatherosclerotic oxazolylmethoxybenzylhydroxyurea thiazolylmethoxybenzylhydroxyurea

IT Antioxidants  
 Bronchodilators  
 Inflammation inhibitors  
 (N-hydroxy-N-[4-(2-phenyloxazolyl- and -thiazolylmethoxy)benzyl]ureas as 5-lipoxygenase inhibitors and inhibitors of oxidative modification of low d. lipoprotein)

IT Antiarteriosclerotics  
 (antiatherosclerotics, N-hydroxy-N-[4-(2-phenyloxazolyl- and -thiazolylmethoxy)benzyl]ureas as 5-lipoxygenase inhibitors and inhibitors of oxidative modification of low d. lipoprotein)

IT Lipoproteins  
 RL: BSU (Biological study, unclassified); BIOL (Biological study) (low-d., N-hydroxy-N-[4-(2-phenyloxazolyl- and -thiazolylmethoxy)benzyl]ureas as 5-lipoxygenase inhibitors and inhibitors of oxidative modification of low d. lipoprotein)

IT 173191-85-0P 173191-87-2P  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)  
 (N-hydroxy-N-[4-(2-phenyloxazolyl- and -thiazolylmethoxy)benzyl]ureas as 5-lipoxygenase inhibitors and inhibitors of oxidative modification of low d. lipoprotein)

IT 173173-26-7P 173173-27-8P 173173-28-9P 173173-29-0P 173173-30-3P  
 173173-31-4P 173173-32-5P 173173-33-6P 173173-34-7P 173173-35-8P  
 173173-36-9P 173173-37-0P 173173-38-1P 173191-80-5P 173191-81-6P  
 173191-82-7P 173191-83-8P 173191-84-9P 173191-86-1P  
 173191-88-3P  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (N-hydroxy-N-[4-(2-phenyloxazolyl- and -thiazolylmethoxy)benzyl]ureas as 5-lipoxygenase inhibitors and inhibitors of oxidative modification of low d. lipoprotein)

IT 80619-02-9, 5-Lipoxygenase  
 RL: BSU (Biological study, unclassified); BIOL (Biological study)  
 (N-hydroxy-N-[4-(2-phenyloxazolyl- and -thiazolylmethoxy)benzyl]ureas as 5-lipoxygenase inhibitors and inhibitors of oxidative modification of low d. lipoprotein)

IT 67-64-1, Acetone, reactions 99-93-4, 4'-Hydroxyacetophenone 110-87-2,  
 Dihydropyran 123-08-0, 4-Hydroxybenzaldehyde 1195-45-5,  
 4-Fluorophenylisocyanate 1198-84-1, DL-4-Hydroxymandelic acid  
 2525-62-4, N-Hexyl isocyanate 30494-97-4, 4-(Chloromethyl)-2-phenyloxazole 103788-61-0, 4-Chloromethyl-5-methyl-2-phenyloxazole  
 141580-65-6, N,O-Bis(carbo-phenoxy)hydroxylamine  
 RL: RCT (Reactant); RACT (Reactant or reagent)  
 (N-hydroxy-N-[4-(2-phenyloxazolyl- and -thiazolylmethoxy)benzyl]ureas as 5-lipoxygenase inhibitors and inhibitors of oxidative modification of low d. lipoprotein)

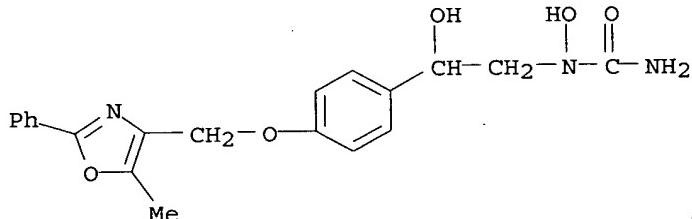
IT 103789-66-8P 103789-67-9P 103789-68-0P 173191-89-4P 173191-90-7P  
 173191-91-8P 173191-92-9P 173191-93-0P 173191-94-1P 173191-95-2P  
 173191-96-3P 173191-97-4P 173191-98-5P 173191-99-6P 173192-00-2P  
 173192-01-3P 173192-02-4P 173192-03-5P 173192-04-6P 173192-05-7P  
 173192-06-8P 173192-07-9P 173192-08-0P 173192-09-1P 173192-10-4P  
 173192-11-5P 173192-12-6P 173192-13-7P 173192-14-8P  
 173192-15-9P 173192-16-0P  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
 (N-hydroxy-N-[4-(2-phenyloxazolyl- and -thiazolylmethoxy)benzyl]ureas as 5-lipoxygenase inhibitors and inhibitors of oxidative modification of low d. lipoprotein)

IT 173191-84-9P  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (N-hydroxy-N-[4-(2-phenyloxazolyl- and -thiazolylmethoxy)benzyl]ureas

as 5-lipoxygenase inhibitors and inhibitors of oxidative modification  
of low d. lipoprotein)

RN 173191-84-9 HCAPLUS

CN Urea, N-hydroxy-N-[2-hydroxy-2-[4-[(5-methyl-2-phenyl-4-oxazolyl)methoxy]phenyl]ethyl]- (9CI) (CA INDEX NAME)

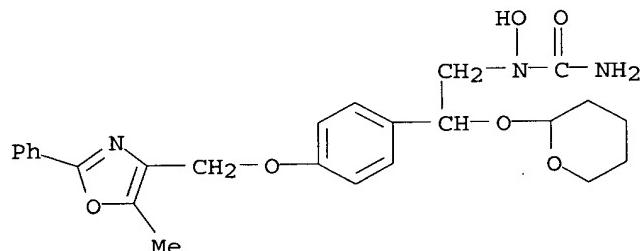


IT 173192-13-7P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT  
(Reactant or reagent)  
(N-hydroxy-N-[4-(2-phenyloxazolyl- and -thiazolylmethoxy)benzyl]ureas  
as 5-lipoxygenase inhibitors and inhibitors of oxidative modification  
of low d. lipoprotein)

RN 173192-13-7 HCAPLUS

CN Urea, N-hydroxy-N-[2-[4-[(5-methyl-2-phenyl-4-oxazolyl)methoxy]phenyl]-2-  
[(tetrahydro-2H-pyran-2-yl)oxy]ethyl]- (9CI) (CA INDEX NAME)



L66 ANSWER 3 OF 26 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 7

ACCESSION NUMBER: 1995:227606 HCAPLUS

DOCUMENT NUMBER: 123:55714

TITLE: Aryl and heteroaryl methoxyphenyl inhibitors of  
leukotriene biosynthesis

INVENTOR(S): Brooks, Dee W.; Kolasa, Teodozy J.

PATENT ASSIGNEE(S): Abbott Laboratories, USA

SOURCE: U.S., 15 pp. Cont.-in-part of U.S. Ser. No. 969,898,  
abandoned.

CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5358955	A	19941025	US 1993-71737	19930602
CA 2136076	AA	19940511	CA 1993-2136076	19931012

WO 9410148	A1	19940511	WO 1993-US9752	19931012
W: CA, JP				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 666849	A1	19950816	EP 1993-923854	19931012
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
JP 08502749	T2	19960326	JP 1993-511096	19931012
PRIORITY APPLN. INFO.:			US 1992-969898	B2 19921030
			US 1993-71737	A 19930602
			WO 1993-US9752	W 19931012

OTHER SOURCE(S): MARPAT 123:55714

ED Entered STN: 06 Dec 1994

AB The present invention relates to a compound of the formula I or a pharmaceutically acceptable salt thereof (wherein W is selected from optionally substituted pyridyl, naphthyl, and quinolyl; dotted line represents optional valence bond; e.g., for single bond, Z = e.g., CO<sub>2</sub>NR<sub>2</sub>R<sub>3</sub>, and for double bond, Z = e.g., :NOCHR<sub>4</sub>CO<sub>2</sub>NR<sub>2</sub>R<sub>3</sub>; A = C<sub>1-6</sub>-alkylene; R<sub>1</sub> = e.g., C<sub>3-8</sub>-cycloalkyl) which inhibits lipoxygenase enzyme activity and leukotriene biosynthesis and is useful in the treatment of inflammatory disease states; also disclosed are leukotriene biosynthesis inhibiting compns. and a method for inhibiting lipoxygenase enzyme activity and leukotriene biosynthesis. In vitro inhibitory potencies against stimulated LTB<sub>4</sub> polymorphonuclear leukocytes: IC<sub>50</sub> ( $\mu$ mol) in the range 0.033-1.65. Inhibition of the biosynthesis of leukotrienes in vivo after oral administration of compound was determined using a

rat peritoneal anaphylaxis model: compds. of this invention prevent the formation of leukotrienes in this model in a range of 1-200  $\mu$ mol/kg. Pharmaceutical compns. were given.

IC ICM C07D215-14

ICS C07D213-30; A61K031-47; A61K031-44

INCL 514311000

CC 27-17 (Heterocyclic Compounds (One Hetero Atom))

Section cross-reference(s): 1, 25, 63

ST leukotriene biosynthesis inhibitor heteroarylmethoxyphenyl arylmethoxyphenyl; lipoxygenase enzyme inhibitor heteroarylmethoxyphenyl arylmethoxyphenyl

IT Leukotrienes

RL: BSU (Biological study, unclassified); BIOL (Biological study) (biosynthesis inhibition; aryl and heteroarylmethoxyphenyl inhibitors of leukotriene biosynthesis)

IT 158606-72-5P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent) (aryl and heteroarylmethoxyphenyl inhibitors of leukotriene biosynthesis)

IT 158606-73-6P 158606-74-7P 158606-77-0P 158606-79-2P 158606-84-9P  
158606-85-0P 158606-88-3P 164578-83-0P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation) (aryl and heteroarylmethoxyphenyl inhibitors of leukotriene biosynthesis)

IT 100-83-4, 3-Hydroxybenzaldehyde 108-85-0, Cyclohexyl bromide 123-08-0  
137-43-9, Bromocyclopentane 524-38-9, N-Hydroxypythalimide 623-51-8,  
Ethyl thioglycolate 939-26-4, 2-(Bromomethyl)naphthalene 2404-35-5,  
Cycloheptyl bromide 3747-74-8, 2-Chloromethylquinoline hydrochloride 6959-47-3, 2-Chloromethylpyridine hydrochloride 13633-25-5,  
1-Bromo-4-phenylbutane 14199-15-6, Methyl 4-hydroxyphenylacetate 64473-35-4 164578-88-5

RL: RCT (Reactant); RACT (Reactant or reagent)  
 (aryl and heteroarylmethoxyphenyl inhibitors of leukotriene biosynthesis)

IT 76529-98-1P, 2-Methoxy-2-(4-hydroxyphenyl)acetic acid methyl ester  
 103119-21-7P 120159-59-3P, 4-(2-Quinolinyl-methoxy)benzaldehyde  
 123723-93-3P, Methyl 4-(quinolin-2-yl-methoxy)phenylacetate 127481-38-3P  
 128253-06-5P 128253-07-6P 128253-08-7P 128253-09-8P 128253-11-2P  
 128253-12-3P 128253-13-4P 128253-14-5P 143055-94-1P 158606-69-0P  
 158606-70-3P 158606-71-4P, 4-(2-Pyridylmethoxy)phenylacetic acid methyl ester 158606-89-4P 158606-90-7P 158606-91-8P 158606-95-2P  
 158606-96-3P 158606-97-4P 158606-98-5P 158606-99-6P 158607-00-2P  
 158607-01-3P 158607-02-4P 158607-03-5P 158607-04-6P 164578-81-8P  
 164578-84-1P 164578-85-2P 164578-86-3P 164578-87-4P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
 (aryl and heteroarylmethoxyphenyl inhibitors of leukotriene biosynthesis)

IT 2550-36-9P, (Bromomethyl)cyclohexane 158606-75-8P 158606-78-1P  
 158606-80-5P 158606-81-6P 158606-82-7P 158606-83-8P  
 158606-87-2P 164578-82-9P

RL: SPN (Synthetic preparation); PREP (Preparation)  
 (aryl and heteroarylmethoxyphenyl inhibitors of leukotriene biosynthesis)

IT 9029-60-1, Lipoxygenase

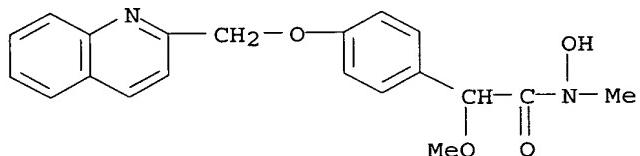
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
 (inhibitors; aryl and heteroarylmethoxyphenyl inhibitors of leukotriene biosynthesis)

IT 158606-81-6P 158606-83-8P

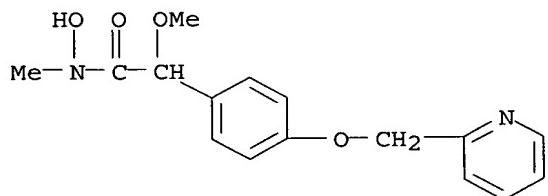
RL: SPN (Synthetic preparation); PREP (Preparation)  
 (aryl and heteroarylmethoxyphenyl inhibitors of leukotriene biosynthesis)

RN 158606-81-6 HCPLUS

CN Benzeneacetamide, N-hydroxy- $\alpha$ -methoxy-N-methyl-4-(2-quinolinylmethoxy)- (9CI) (CA INDEX NAME)



RN 158606-83-8 HCPLUS  
 CN Benzeneacetamide, N-hydroxy- $\alpha$ -methoxy-N-methyl-4-(2-pyridinylmethoxy)- (9CI) (CA INDEX NAME)



L66 ANSWER 4 OF 26 HCPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 8  
 ACCESSION NUMBER: 1995:277045 HCPLUS  
 DOCUMENT NUMBER: 122:46487  
 TITLE: CAT-1 inhibitors, their synthesis, pharmaceutical compositions, and methods of use  
 INVENTOR(S): Guthrie, Robert W.; Mullin, John G., Jr.; Kachensky, David F.; Kierstead, Richard W.; Tilley, Jefferson W.; Heathers, Guy P.; Higgins, Alan J.; Lemahieu, Ronald A.  
 PATENT ASSIGNEE(S): Hoffman-La Roche Inc., USA  
 SOURCE: U.S., 85 pp. Cont.-in-part of U.S. Ser. No. 698, 014, abandoned.  
 CODEN: USXXAM  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 2  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5344843	A	19940906	US 1992-850620	19920313
RU 2059603	C1	19960510	RU 1992-5011784	19920131
EP 512352	A2	19921111	EP 1992-107135	19920427
EP 512352	A3	19930310		
EP 512352	B1	19960327		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, MC, NL, PT, SE				
AT 136018	E	19960415	AT 1992-107135	19920427
AU 9216003	A1	19921112	AU 1992-16003	19920504
AU 653398	B2	19940929		
CA 2068076	AA	19921110	CA 1992-2068076	19920506
ZA 9203279	A	19930127	ZA 1992-3279	19920506
NO 9201840	A	19921110	NO 1992-1840	19920508
HU 63602	A2	19930928	HU 1992-1538	19920508
JP 05279353	A2	19931026	JP 1992-143375	19920508
JP 07107060	B4	19951115		
RO 109938	B1	19950728	RO 1992-622	19920508
BR 9201769	A	19921229	BR 1992-1769	19920511
PRIORITY APPLN. INFO.:			US 1991-698014	B2 19910509
			US 1992-850620	A 19920313

OTHER SOURCE(S): MARPAT 122:46487

ED Entered STN: 07 Jan 1995

AB The invention relates to compds. I (R1 = OH; R2, R3 = H, alkyl, aryl, alkoxy, etc.; X, Y together = O, or one is amino and other is H; Z = S, CR2=CR2'; A = bond, O, S, SO, CHCH, etc.; B = bond, O, S, SO, etc.; Q = Ph, cyclohexyl, pyridinyl, etc.; n = 1-6) and their pharmaceutically acceptable salts, and when appropriate, enantiomers, racemates, diastereomers or mixts. thereof or geometric isomer or mixts. thereof, and pharmaceutically acceptable salts thereof. The compds. inhibit carnitine acyltransferase 1 (CAT-1) and are therefore useful in the prevention of injury to ischemic tissue, and can limit infarct size, improve cardiac function and prevent arrhythmias during and following a myocardial infarction. 5-[[2-(2-Naphthalenyl)ethyl]oxy]- $\alpha$ -oxo-2-thiopheneacetic acid (preparation given) inhibited CAT-1 with an IC50 = 0.05  $\mu$ M. Tablet and capsule formulations containing 4-[2-(2-naphthyl)ethoxy]- $\alpha$ -oxobenzeneacetic acid are presented.

IC ICM A61K031-19  
 ICS A61K031-38; C07C065-40; C07D333-32

INCL 514473000

CC 1-8 (Pharmacology)

Section cross-reference(s): 7, 25, 27, 63

ST carnitine acyltransferase inhibitor compd; ischemia carnitine  
acyltransferase inhibitor

IT Ischemia  
(synthesis and pharmaceutical compns. and use of carnitine  
acyltransferase inhibitor compds. for prevention of injury from)

IT Pharmaceutical dosage forms  
(capsules, synthesis and pharmaceutical compns. and use of carnitine  
acyltransferase inhibitor compds.)

IT Heart, disease  
(infarction, synthesis and pharmaceutical compns. and use of carnitine  
acyltransferase inhibitor compds. for prevention of injury from)

IT Pharmaceutical dosage forms  
(tablets, synthesis and pharmaceutical compns. and use of carnitine  
acyltransferase inhibitor compds.)

IT 39386-49-7, Carnitine acyltransferase  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological  
study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES  
(Uses)  
(inhibitor compds.; synthesis and pharmaceutical compns. and use of  
carnitine acyltransferase inhibitor compds.)

IT 145794-10-1P 145795-19-3P 145795-25-1P 145795-27-3P 145795-76-2P  
145795-81-9P  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological  
study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU  
(Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT  
(Reactant or reagent); USES (Uses)  
(synthesis and pharmaceutical compns. and use of carnitine  
acyltransferase inhibitor compds.)

IT 145794-12-3P 145794-14-5P 145794-16-7P 145794-21-4P 145794-23-6P  
145794-25-8P 145794-27-0P 145794-29-2P 145794-31-6P 145794-33-8P  
145794-35-0P 145794-37-2P 145794-39-4P 145794-41-8P 145794-43-0P  
145794-45-2P 145794-47-4P 145794-49-6P 145794-51-0P 145794-53-2P  
145794-55-4P 145794-57-6P 145794-59-8P 145794-61-2P 145794-63-4P  
145794-65-6P 145794-67-8P 145794-69-0P 145794-71-4P 145794-73-6P  
145794-75-8P 145794-77-0P 145794-79-2P 145794-82-7P 145794-86-1P  
145794-90-7P 145794-92-9P 145794-94-1P 145794-98-5P 145794-99-6P  
145795-01-3P 145795-02-4P 145795-04-6P 145795-05-7P 145795-06-8P  
145795-07-9P 145795-08-0P 145795-09-1P 145795-10-4P 145795-11-5P  
145795-12-6P 145795-13-7P 145795-14-8P 145795-15-9P 145795-16-0P  
145795-18-2P 145795-20-6P 145795-21-7P 145795-23-9P 145795-24-0P  
145795-26-2P 145795-28-4P 145795-32-0P 145795-33-1P 145795-34-2P  
145795-38-6P 145795-39-7P 145795-41-1P 145795-43-3P 145795-44-4P  
145795-45-5P 145795-46-6P 145795-47-7P 145795-48-8P 145795-49-9P  
145795-50-2P 145795-51-3P 145795-52-4P 145795-53-5P 145795-55-7P  
145795-56-8P 145795-57-9P 145795-58-0P 145795-59-1P 145795-60-4P  
145795-65-9P 145795-66-0P 145795-70-6P 145795-71-7P 145795-72-8P  
145795-73-9P 145795-74-0P 145795-75-1P 145795-77-3P 145795-79-5P  
145795-82-0P 145795-83-1P 145795-84-2P 145795-85-3P 145795-86-4P  
145795-87-5P 145795-88-6P 145795-89-7P 145795-90-0P 145795-91-1P  
145795-92-2P 145796-00-5P 145796-01-6P 145796-02-7P 145796-03-8P  
145796-04-9P 145796-05-0P 145796-06-1P 145796-07-2P 145796-08-3P  
145797-00-8P 146548-36-9P 146548-37-0P 146548-40-5P 146548-41-6P  
146548-42-7P 146548-43-8P 146548-44-9P 146572-66-9P 160062-09-9P  
160062-10-2P 160062-11-3P 160062-12-4P 160062-13-5P 160062-14-6P  
160062-15-7P 160062-17-9P 160062-18-0P 160062-19-1P 160062-20-4P  
160062-21-5P 160062-22-6P 160062-23-7P 160062-24-8P  
160062-25-9P 160062-26-0P  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological  
study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use);  
BIOL (Biological study); PREP (Preparation); USES (Uses)

(synthesis and pharmaceutical compns. and use of carnitine acyltransferase inhibitor compds.)

IT 145794-09-8 145795-95-5  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (synthesis and pharmaceutical compns. and use of carnitine acyltransferase inhibitor compds.)  
 IT 56-81-5, 1,2,3-Propanetriol, reactions 57-14-7, 1,1-Dimethylhydrazine 79-37-8, Oxalyl chloride 91-21-4, 1,2,3,4-Tetrahydroisoquinoline 92-44-4, 2,3-Dihydroxynaphthalene 93-20-9 100-39-0, Benzyl bromide 108-00-9, N,N-Dimethylethylenediamine 108-01-0 111-42-2, Diethanolamine, reactions 112-27-6 124-40-3, Dimethylamine, reactions 141-43-5, reactions 403-14-5, 3-Fluoro-4-hydroxyacetophenone 460-00-4, 4-Fluorobromobenzene 588-63-6, (3-Bromopropoxy)benzene 589-10-6, β-Bromophenetole 593-56-6, Methoxylamine hydrochloride 613-54-7, Bromomethyl 2-naphthyl ketone 637-59-2, 3-Bromo-1-phenylpropane 769-39-1, 2,3,5,6-Tetrafluorophenol 875-59-2, 4-Hydroxy-2-methylacetophenone 876-02-8, 4-Hydroxy-3-methylacetophenone 937-14-4, 3-Chloroperbenzoic acid 939-26-4, 2-Bromomethylnaphthalene 1137-41-3, p-Aminobenzophenone 1200-03-9, (4-Bromobutoxy)benzene 1940-28-9, 4-Bromo-3,5-dichlorophenol 2243-83-6, 2-Naphthoyl chloride 2450-71-7, Propargylamine 2478-38-8, 3,5-Dimethoxy-4-hydroxyacetophenone 2605-67-6, (Carbomethoxymethylene)triphenylphosphorane 2687-12-9, (3-Chloro-1-propenyl)benzene 2687-43-6 2892-29-7, 3-Chloro-4-hydroxyacetophenone 2967-54-6, 3,5-Difluoro-4-hydroxybenzonitrile 3245-62-3 3332-29-4 3747-74-8, 2-Chloromethylquinoline hydrochloride 3814-20-8 4229-44-1, N-Methylhydroxylamine hydrochloride 4442-79-9, Cyclohexaneethanol 4755-77-5, Ethyl oxalyl chloride 5264-15-3, 4-Pyridinebutanol 5452-37-9, Cyclooctylamine 5470-11-1, Hydroxylamine hydrochloride 5856-77-9, 2,2-Dimethylbutyryl chloride 6089-04-9 6315-52-2 6322-56-1, 4-Hydroxy-3-nitroacetophenone 6707-01-3, Chloromethoxybenzene 7664-41-7, Ammonia, reactions 13246-14-5 16427-44-4 16839-97-7 17044-70-1, 3,5-Dichloro-4-hydroxyacetophenone 20009-28-3 20020-27-3 21087-29-6 21886-62-4 22118-09-8, Bromoacetyl chloride 22921-72-8 23287-26-5 23314-24-1 24484-55-7 27064-92-2 31076-84-3 32462-30-9, (S)-4-Hydroxyphenylglycine 34604-52-9 36754-60-6, 2-Chloromethylbenzofuran 37595-74-7 38078-09-0, Diethylaminosulfur trifluoride 38250-16-7 38945-21-0 39199-93-4 39500-31-7 40299-87-4, 4-(Bromoacetyl)morpholine 40786-20-7 40926-77-0 41656-75-1 51795-97-2 53542-78-2 54537-30-3 60753-14-2, 3-Pyridinebutanol 61236-14-4 62001-72-3 63649-88-7 63649-90-1 63650-21-5 64957-86-4 65512-08-5 66340-55-4 68301-59-7 69189-03-3 70080-54-5 76469-33-5 77923-27-4, 2-(Cyclooctyloxy)ethanol 86902-13-8 87271-22-5 87723-22-6, 2-(4-Bromobutoxy)naphthalene 91540-82-8 93957-49-4 98619-07-9 98793-02-3 99690-59-2 107890-32-4 109083-77-4 113272-40-5 120895-36-5 123843-57-2, 2,6-Difluoro-4-hydroxybenzonitrile 128988-59-0 130954-91-5 132464-59-6 141482-06-6 145794-07-6 145794-08-7 145794-87-2 145794-88-3 145795-03-5 145796-98-1 145797-06-4 145797-56-4 145798-06-7 145798-30-7 145798-31-8 145798-32-9 145798-34-1 145798-35-2 145798-36-3 145798-37-4 145798-38-5 145798-39-6 145798-40-9 145798-42-1 145798-43-2 145798-44-3 145798-45-4 145798-46-5 145798-47-6 145798-49-8 145798-50-1 145798-51-2 145798-52-3 145798-53-4 145798-54-5 145798-55-6 145798-56-7 145798-57-8 145798-58-9 145798-59-0 145798-60-3 145798-61-4 145798-62-5 145798-63-6 145798-64-7 145798-65-8 160062-29-3 160062-43-1 160062-44-2D, γ-oxo-2-naphthalenebutanoic acid 160062-46-4 160062-47-5

RL: RCT (Reactant); RACT (Reactant or reagent)  
 (synthesis and pharmaceutical compns. and use of carnitine  
 acyltransferase inhibitor compds.)

IT	69651-48-5P	89012-04-4P	101125-34-2P	131003-09-3P	134748-95-1P
	145794-11-2P	145794-13-4P	145794-15-6P	145794-17-8P	145794-19-0P
	145794-22-5P	145794-24-7P	145794-26-9P	145794-28-1P	145794-30-5P
	145794-32-7P	145794-34-9P	145794-36-1P	145794-38-3P	145794-40-7P
	145794-42-9P	145794-44-1P	145794-46-3P	145794-48-5P	145794-50-9P
	145794-52-1P	145794-54-3P	145794-56-5P	145794-58-7P	145794-60-1P
	145794-62-3P	145794-64-5P	145794-66-7P	145794-68-9P	145794-70-3P
	145794-72-5P	145794-74-7P	145794-76-9P	145794-78-1P	145794-81-6P
	145794-83-8P	145794-85-0P	145794-89-4P	145794-91-8P	145794-93-0P
	145795-00-2P	145795-29-5P	145795-31-9P	145795-61-5P	145795-62-6P
	145795-64-8P	145795-68-2P	145795-69-3P	145796-75-4P	145796-76-5P
	145796-77-6P	145796-79-8P	145796-81-2P	145796-82-3P	145796-83-4P
	145796-84-5P	145796-86-7P	145796-87-8P	145796-88-9P	145796-89-0P
	145796-90-3P	145796-91-4P	145796-92-5P	145796-93-6P	145796-94-7P
	145796-95-8P	145796-96-9P	145796-97-0P	145796-99-2P	145797-01-9P
	145797-02-0P	145797-03-1P	145797-04-2P	145797-05-3P	145797-07-5P
	145797-08-6P	145797-09-7P	145797-10-0P	145797-11-1P	145797-12-2P
	145797-13-3P	145797-14-4P	145797-15-5P	145797-16-6P	145797-17-7P
	145797-18-8P	145797-19-9P	145797-20-2P	145797-21-3P	145797-22-4P
	145797-23-5P	145797-24-6P	145797-25-7P	145797-26-8P	145797-27-9P
	145797-28-0P	145797-29-1P	145797-30-4P	145797-31-5P	145797-32-6P
	145797-33-7P	145797-34-8P	145797-35-9P	145797-36-0P	145797-37-1P
	145797-38-2P	145797-39-3P	145797-40-6P	145797-41-7P	145797-42-8P
	145797-43-9P	145797-44-0P	145797-45-1P	145797-46-2P	145797-47-3P
	145797-48-4P	145797-49-5P	145797-50-8P	145797-51-9P	145797-52-0P
	145797-55-3P	145797-57-5P	145797-58-6P	145797-59-7P	145797-60-0P
	145797-61-1P	145797-62-2P	145797-63-3P	145797-65-5P	145797-66-6P
	145797-67-7P	145797-68-8P	145797-69-9P	145797-70-2P	145797-71-3P
	145797-72-4P	145797-73-5P	145797-74-6P	145797-75-7P	145797-76-8P
	145797-77-9P	145797-78-0P	145797-79-1P	145797-80-4P	145797-81-5P
	145797-82-6P	145797-83-7P	145797-84-8P	145797-85-9P	145797-86-0P
	145797-87-1P	145797-89-3P	145797-90-6P	145797-92-8P	145797-93-9P
	145797-94-0P	145797-95-1P	145797-96-2P	145797-97-3P	145797-98-4P
	145797-99-5P	145798-00-1P	145798-01-2P	145798-02-3P	145798-03-4P
	145798-04-5P	145798-05-6P	145798-07-8P	145798-08-9P	145798-09-0P
	145798-10-3P	145798-11-4P	145798-12-5P	145798-13-6P	145798-14-7P
	145798-15-8P	145798-16-9P	145798-17-0P	145798-18-1P	145798-19-2P
	145798-20-5P	145798-21-6P	145798-22-7P	145798-23-8P	145798-24-9P
	145798-26-1P	145798-27-2P	145798-28-3P	146548-38-1P	160062-27-1P
	160062-28-2P	160062-31-7P	160062-32-8P	160062-33-9P	160062-34-0P
	160062-35-1P	160062-36-2P	160062-37-3P	160062-38-4P	160062-39-5P
	160062-40-8P	160062-41-9P	160062-42-0P		

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(synthesis and pharmaceutical compns. and use of carnitine acyltransferase inhibitor compds.)

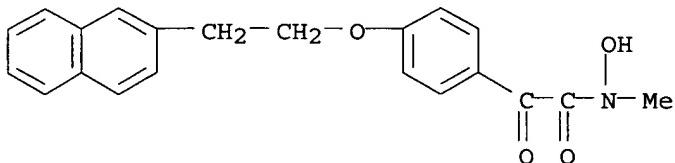
IT	145794-20-3P	145795-17-1P	145795-22-8P	145795-35-3P	145795-36-4P
	145795-37-5P	145795-40-0P	145795-54-6P	145795-67-1P	145796-09-4P
	145796-80-1P	145796-85-6P	145798-25-0P	146548-39-2P	160062-30-6P

RL: SPN (Synthetic preparation); PREP (Preparation)

(synthesis and pharmaceutical compns. and use of carnitine acyltransferase inhibitor compds.)

IT	160062-21-5P				
	RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)				
	(synthesis and pharmaceutical compns. and use of carnitine acyltransferase inhibitor compds.)				

acyltransferase inhibitor compds.)  
 RN 160062-21-5 HCPLUS  
 CN Benzeneacetamide, N-hydroxy-N-methyl-4-[2-(2-naphthalenyl)ethoxy]- $\alpha$ -oxo- (9CI) (CA INDEX NAME)



L66 ANSWER 5 OF 26 HCPLUS COPYRIGHT 2005 ACS on STM  
 ACCESSION NUMBER: 2002:964135 HCPLUS  
 DOCUMENT NUMBER: 138:24543  
 TITLE: Preparation of benzyloxyphenyloxobutyrates and related compounds for the treatment of metabolic disorders  
 INVENTOR(S): Sharma, Shalini; Von Borstel, Reid W.; Hodge, Kirvin L.  
 PATENT ASSIGNEE(S): Wellstat Therapeutics Corporation, USA; Bamat, Michael K.  
 SOURCE: PCT Int. Appl., 242 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002100341	A2	20021219	WO 2002-US18388	20020612
WO 2002100341	A3	20040701		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2450221	AA	20021219	CA 2002-2450221	20020612
US 2003149107	A1	20030807	US 2002-167839	20020612
EP 1461323	A2	20040929	EP 2002-744271	20020612
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY, TR				
JP 2005501012	T2	20050113	JP 2003-503168	20020612
US 2004077896	A1	20040422	US 2003-684644	20031014
US 6924314	B2	20050802		
US 2004092518	A1	20040513	US 2003-684735	20031014
US 2004092516	A1	20040513	US 2003-685183	20031014
US 6946491	B2	20050920		
US 2004097585	A1	20040520	US 2003-684730	20031014
US 6916848	B2	20050712		
US 2004236100	A1	20041125	US 2003-684660	20031014
US 6858602	B2	20050222		

US 2004267025	A1	20041230	US 2003-684740	20031014
US 2004242692	A1	20041202	US 2004-865088	20040610
US 2005004115	A1	20050106	US 2004-892950	20040716
US 2005090555	A1	20050428	US 2004-5449	20041206
<b>PRIORITY APPLN. INFO.:)</b>				
US 2001-297282P P 20010612				
<US 2002-167839 A3 20020612				
WO 2002-US18388 W 20020612				
US 2003-685183 A3 20031014				
US 2004-865088 A1 20040610				

OTHER SOURCE(S) : MARPAT 138:24543

ED Entered STN: 20 Dec 2002

AB Biol. active title compds. [I; n = 1, 2; m, q, p = 0, 1; R5 = alkyl; R9 = H, halo, alkoxy; A = (halo-, alkyl-, perfluoromethyl-, alkoxy-, perfluoromethoxy-substituted) Ph, (Me-, Et-substituted) cycloalkyl, 5-6 membered heteroarom. ring having 1-2 N, S, O atoms; X = CH<sub>2</sub>, Q = OR<sub>1</sub>, R<sub>1</sub> = Et; or X = CH<sub>2</sub>CR<sub>1</sub>R<sub>13</sub>, CH<sub>2</sub>CH(NHAc), Q = OR<sub>1</sub>, R<sub>1</sub> = H, alkyl; or X = CH<sub>2</sub>CH<sub>2</sub>, Q = NR<sub>1</sub>OR<sub>11</sub>; R<sub>12</sub>, R<sub>13</sub> = H, Me; 1 of R<sub>10</sub>, R<sub>11</sub> = H, alkyl, OH, the other = H, alkyl], were prepared Thus, 4-(2-fluorobenzyl)acetophenone (preparation given) in THF and DMPU was treated with a solution of Li bis(trimethylsilyl)amide at -60°; after 10 min, tert-Bu bromoacetate was added followed by stirring for an addnl. 10 min and warming to room temperature for 4 h to give tert-Bu 4-[4-(2-fluorobenzyl)phenyl]-4-oxobutyrate. The latter was stirred with CF<sub>3</sub>CO<sub>2</sub>H in CH<sub>2</sub>C<sub>12</sub> to give 4-[4-(2-fluorobenzyl)phenyl]-4-oxobutyric acid. Tested I showed antidiabetic activity in a variety of tests. I are useful in treatment of various metabolic disorders such as insulin resistance syndrome, diabetes, hyperlipidemia, fatty liver disease, cachexia, obesity, atherosclerosis and arteriosclerosis.

IC ICM A61K

CC 25-17 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)

Section cross-reference(s): 1, 27, 28

ST benzyloxyphenyloxobutyrate prepn metabolic disorder treatment; diabetes mellitus fatty liver hyperlipidemia treatment benzyloxyphenyloxobutyrate; cachexia obesity atherosclerosis hypertension arteriosclerosis treatment benzyloxyphenyloxobutyrate prepn; nephropathy neuropathy retinopathy foot ulceration cataract treatment benzyloxyphenyloxobutyrate prepn

IT Liver, disease  
(fatty, treatment; preparation of benzyloxyphenyloxobutyrates and related compds. for treatment of metabolic disorders)

IT Foot  
(foot ulceration treatment; preparation of benzyloxyphenyloxobutyrates and related compds. for treatment of metabolic disorders)

IT Lipids, biological studies  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(hyperlipidemia, treatment; preparation of benzyloxyphenyloxobutyrates and related compds. for treatment of metabolic disorders)

IT Autoimmune disease  
(insulin-dependent diabetes mellitus, treatment; preparation of benzyloxyphenyloxobutyrates and related compds. for treatment of metabolic disorders)

IT Diabetes mellitus  
(insulin-dependent, treatment; preparation of benzyloxyphenyloxobutyrates and related compds. for treatment of metabolic disorders)

IT Nerve, disease  
(neuropathy, treatment; preparation of benzyloxyphenyloxobutyrates and related compds. for treatment of metabolic disorders)

IT Antiarteriosclerotics  
Antidiabetic agents  
Antihypertensives

Antiobesity agents

Human

Hypolipemic agents

(preparation of benzyloxyphenyloxobutyrates and related compds. for treatment of metabolic disorders)

IT Eye, disease

(retinopathy, treatment; preparation of benzyloxyphenyloxobutyrates and related compds. for treatment of metabolic disorders)

IT Arteriosclerosis

Atherosclerosis

Cachexia

Cataract

Diabetes mellitus

Hypertension

Kidney, disease

Obesity

(treatment; preparation of benzyloxyphenyloxobutyrates and related compds. for treatment of metabolic disorders)

IT 478162-80-0P

RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(preparation of benzyloxyphenyloxobutyrates and related compds. for treatment of metabolic disorders)

IT 6686-25-5P 478162-45-7P 478162-46-8P 478162-47-9P 478162-48-0P

478162-49-1P 478162-50-4P 478162-51-5P 478162-52-6P 478162-53-7P

478162-54-8P 478162-55-9P 478162-56-0P 478162-57-1P 478162-58-2P

478162-59-3P 478162-60-6P 478162-61-7P 478162-62-8P 478162-63-9P

478162-64-0P 478162-65-1P 478162-66-2P 478162-67-3P 478162-68-4P

478162-69-5P 478162-70-8P 478162-71-9P 478162-72-0P 478162-73-1P

478162-74-2P 478162-75-3P 478162-76-4P 478162-77-5P 478162-78-6P

478162-79-7P 478162-81-1P 478162-82-2P 478162-83-3P 478162-84-4P

478162-85-5P 478162-86-6P 478162-87-7P 478162-88-8P 478162-89-9P

478162-90-2P 478162-91-3P 478162-92-4P 478162-93-5P

478162-94-6P 478162-95-7P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of benzyloxyphenyloxobutyrates and related compds. for treatment of metabolic disorders)

IT 89-92-9, 2-Methylbenzyl bromide 99-93-4, 4-Hydroxyacetophenone

100-44-7, Benzyl chloride, reactions 105-36-2, Ethyl bromoacetate

109-83-1, 2-Methylaminoethanol 118-93-4 121-71-1 395-44-8,

2-Trifluoromethylbenzyl bromide 402-49-3, 4-Trifluoromethylbenzyl

bromide 446-48-0, 2-Fluorobenzyl bromide 446-51-5, 2-Fluorobenzyl

alcohol 456-41-7, 3-Fluorobenzyl bromide 459-46-1, 4-Fluorobenzyl

bromide 600-00-0, Ethyl 2-bromoisobutyrate 611-17-6, 2-Chlorobenzyl

bromide 612-16-8, 2-Methoxybenzyl alcohol 623-05-2, 4-Hydroxybenzyl

alcohol 632-46-2, 2,6-Dimethylbenzoic acid 824-45-3,

2,5-Dimethylbenzyl chloride 1068-90-2, Diethyl acetamidomalonate

2033-24-1, Meldrum's acid 3179-31-5, 1,2,4-Triazole-3-thiol 5292-43-3,

tert-Butyl bromoacetate 5402-55-1, 2-(2-Thienyl)ethanol 5466-06-8,

Ethyl 3-mercaptopropionate 6959-47-3, 2-Picolyl chloride hydrochloride

7051-34-5, Cyclopropylmethyl bromide 13670-99-0, 2,6-

Difluoroacetophenone 14191-95-8, 4-Hydroxybenzyl cyanide 16475-90-4,

Methyl 2-hydroxy-5-acetylbenzoate 17247-58-4, Cyclobutylmethyl bromide

23915-07-3, 2,4-Difluorobenzyl bromide 50919-06-7 85117-99-3,

2,5-Difluorobenzyl bromide 85118-00-9, 2,6-Difluorobenzyl bromide

90259-27-1, 2-Fluoro-6-methylbenzoic acid 478163-47-2

RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation of benzyloxyphenyloxobutyrates and related compds. for treatment of metabolic disorders)

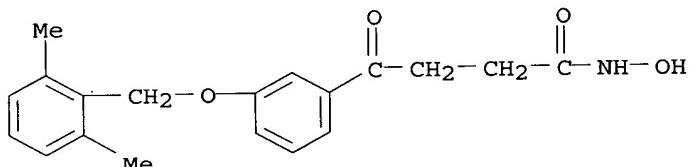
IT 17138-28-2P 39971-36-3P, Methyl 2-methoxy-5-acetylbenzoate 50596-33-3P  
 54696-05-8P, 4-(Benzyl)acetophenone 62285-58-9P, 2,6-Dimethylbenzyl Alcohol 68535-61-5P, 2-Methoxy-5-acetylbenzoic acid 72293-94-8P  
 72293-95-9P 72293-96-0P 74788-82-2P, 2,6-DimethylbenzylAmine 93291-55-5P 93291-62-4P 93748-83-5P 130403-21-3P,  
 N- (2,6-Dimethylbenzyl)phthalimide 170916-37-7P 187532-78-1P  
 187532-79-2P 187532-84-9P 312592-47-5P 478159-56-7P 478162-96-8P  
 478162-97-9P 478162-98-0P 478162-99-1P 478163-00-7P 478163-01-8P  
 478163-02-9P 478163-03-0P 478163-04-1P 478163-05-2P 478163-06-3P  
 478163-07-4P 478163-08-5P 478163-09-6P 478163-10-9P 478163-11-0P  
 478163-12-1P 478163-13-2P 478163-14-3P 478163-15-4P 478163-16-5P  
 478163-17-6P 478163-18-7P 478163-19-8P 478163-20-1P 478163-21-2P  
 478163-22-3P 478163-23-4P 478163-24-5P 478163-25-6P 478163-26-7P  
 478163-27-8P 478163-28-9P 478163-29-0P 478163-30-3P 478163-31-4P  
 478163-32-5P 478163-33-6P 478163-34-7P 478163-35-8P 478163-36-9P  
 478163-37-0P 478163-38-1P 478163-39-2P 478163-40-5P 478163-41-6P  
 478163-42-7P 478163-43-8P 478163-44-9P 478163-45-0P 478163-46-1P  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of benzyloxyphenyloxobutyrates and related compds. for treatment of metabolic disorders)

IT 9004-10-8, Insulin, biological studies  
 RL: BSU (Biological study, unclassified); BIOL (Biological study)  
 (resistance, treatment; preparation of benzyloxyphenyloxobutyrates and related compds. for treatment of metabolic disorders)

IT 478162-92-4P  
 RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (preparation of benzyloxyphenyloxobutyrates and related compds. for treatment of metabolic disorders)

RN 478162-92-4 HCPLUS  
 CN Benzenebutanamide, 3-[(2,6-dimethylphenyl)methoxy]-N-hydroxy- $\gamma$ -oxo- (9CI) (CA INDEX NAME)



L66 ANSWER 6 OF 26 HCPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1994:655667 HCPLUS  
 DOCUMENT NUMBER: 121:255667  
 TITLE: Aryl- and heteroarylmethoxyphenyl inhibitors of leukotriene biosynthesis  
 INVENTOR(S): Brooks, Dee W.; Kolasa, Teodozy  
 PATENT ASSIGNEE(S): Abbott Laboratories, USA  
 SOURCE: PCT Int. Appl., 40 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 2

## PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9410148	A1	19940511	WO 1993-US9752	19931012
W: CA, JP RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 5358955	A	19941025	US 1993-71737	19930602
EP 666849	A1	19950816	EP 1993-923854	19931012
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
JP 08502749	T2	19960326	JP 1993-511096 US 1992-969898 US 1993-71737 WO 1993-US9752	19931012 A 19921030 A 19930602 W 19931012

PRIORITY APPLN. INFO.:

OTHER SOURCE(S): MARPAT 121:255667

ED Entered STN: 26 Nov 1994

AB The invention relates to compds. I and pharmaceutically acceptable salts [wherein A = C1-6 alkylene; R1 = (un)substituted cycloalkyl, alkoxy, PhO, pyridyloxy, Ph, pyridyl, thieryl, furyl, benzofuryl, benzothienyl, or thiazoyl; Z = (singly bound) COONR2R3, CON(OH)R2, OCHR4COONR2R3, SCHR4CON(OH)R2, ON:CHCOONR2R3, (doubly bound) :NOCHR4COONR2R3, etc.; R2, R3, R4 = H, alkyl, hydroxyalkyl; Y = H, alkyl, alkoxy, PhO, halo; n = 0-4; W = (un)substituted pyridyl, naphthyl, or quinolyl]. I inhibit lipoxygenase enzyme activity and leukotriene biosynthesis, and are useful in the treatment of inflammatory disease states. For example, Me 4-(2-quinolylmethoxy)phenylacetate (preparation given) underwent  $\alpha$ -alkylation using NaH and cyclohexyl bromide, followed by hydrolysis using NaOH in refluxing MeOH, to give 2-cyclohexyl-2-[4-(2-quinolylmethoxy)phenyl]acetic acid. This was converted with ClCO2Bu-iso and Et3N to a mixed anhydride, which then reacted with MeNHOSiMe3 (prepared in situ) to give upon workup title compound II. The IC50 of II for inhibition of Ca ionophore-stimulated LTB4 formation in human polymorphonuclear leukocytes in vitro was 0.033  $\mu$ M.

IC ICM C07D213-30

ICS C07D215-02; A61K031-44; A61K031-47

CC 27-17 (Heterocyclic Compounds (One Hetero Atom))

Section cross-reference(s): 1

ST hydroxyamide pyridylmethoxyphenyl prepn lipoxygenase inhibitor; quinolinylmethoxyphenyl hydroxyamide prepn leukotriene biosynthesis inhibitor; naphthylmethoxyphenyl hydroxyamide prepn antiinflammatory antiallergic

IT Allergy inhibitors

Inflammation inhibitors  
(aryl- and heteroaryl methoxyphenyl-containing hydroxyamides)

IT Leukotrienes

RL: BPN (Biosynthetic preparation); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)  
(biosynthesis of, inhibitors of, aryl- and heteroaryl methoxyphenyl-containing hydroxyamides as)

IT 13633-25-5, 1-Bromo-4-phenylbutane 158607-05-7, 1-Bromo-4-(4-chlorophenyl)butane

RL: RCT (Reactant); RACT (Reactant or reagent)  
(Grignard reaction of, in preparation of (hetero)aryl-containing hydroxyamides as lipoxygenase inhibitors)

IT 4229-44-1, N-Methylhydroxylamine hydrochloride

RL: RCT (Reactant); RACT (Reactant or reagent)  
(amidation of, in preparation of (hetero)aryl-containing hydroxyamides as lipoxygenase inhibitors)

IT 71160-24-2P, LTB4

RL: BPN (Biosynthetic preparation); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)  
 (biosynthesis of, inhibitors of, aryl- and heteroarylmethoxyphenyl-containing hydroxyamides as)

IT 1198-84-1, 4-Hydroxymandelic acid 16645-06-0, N,N-Dimethylhydroxylamine hydrochloride  
 RL: RCT (Reactant); RACT (Reactant or reagent)  
 (esterification of, in preparation of (hetero)aryl-containing hydroxyamides as  
 lipoxygenase inhibitors)

IT 100-83-4, 3-Hydroxybenzaldehyde 123-08-0, 4-Hydroxybenzaldehyde  
 524-38-9, N-Hydroxyphthalimide 939-26-4, 2-(Bromomethyl)naphthalene  
 3747-74-8, 2-Chloromethylquinoline hydrochloride 6959-47-3,  
 2-Chloromethylpyridine hydrochloride 14199-15-6, Methyl  
 4-hydroxyphenylacetate  
 RL: RCT (Reactant); RACT (Reactant or reagent)  
 (etherification of, in preparation of (hetero)aryl-containing hydroxyamides as  
 lipoxygenase inhibitors)

IT 63551-74-6  
 RL: RCT (Reactant); RACT (Reactant or reagent)  
 (inhibitors of, aryl- and heteroarylmethoxyphenyl-containing hydroxyamides as)

IT 2921-14-4, Carboxymethoxylamine hemihydrochloride 20295-82-3,  
 Aminooxyacetic acid hydrochloride  
 RL: RCT (Reactant); RACT (Reactant or reagent)  
 (oxidation by, in preparation of (hetero)aryl-containing hydroxyamides as  
 lipoxygenase inhibitors)

IT 298-12-4  
 RL: RCT (Reactant); RACT (Reactant or reagent)  
 (oxidation of, in preparation of (hetero)aryl-containing hydroxyamides as  
 lipoxygenase inhibitors)

IT 76529-98-1P, 2-Methoxy-2-(4-hydroxyphenyl)acetic acid methyl ester  
 120159-59-3P, 4-(2-Quinolinylmethoxy)benzaldehyde 123723-93-3P, Methyl  
 4-(2-quinolinylmethoxy)phenylacetate 127481-38-3P 128253-06-5P  
 128253-07-6P 128253-08-7P, 2-Cyclohexyl-2-[4-(2-  
 quinolinylmethoxy)phenyl]acetic acid methyl ester 128253-09-8P,  
 2-Cycloheptyl-2-[4-(2-quinolinylmethoxy)phenyl]acetic acid methyl ester  
 128253-11-2P 128253-12-3P 128253-13-4P, 2-Cyclohexyl-2-[4-(2-  
 quinolinylmethoxy)phenyl]acetic acid 128253-14-5P, 2-Cycloheptyl-2-[4-(2-  
 quinolinylmethoxy)phenyl]acetic acid 131340-67-5P, 3-(2-  
 Naphthylmethoxy)benzaldehyde 143055-94-1P 158606-69-0P,  
 2-Methoxy-2-[4-(2-quinolinylmethoxy)phenyl]acetic acid methyl ester  
 158606-70-3P, 2-Methoxy-2-[4-(2-quinolinylmethoxy)phenyl]acetic acid  
 158606-71-4P, 4-(2-Pyridylmethoxy)phenylacetic acid methyl ester  
 158606-89-4P 158606-90-7P 158606-91-8P 158606-92-9P 158606-93-0P  
 158606-94-1P 158606-95-2P 158606-96-3P 158606-97-4P 158606-98-5P  
 158606-99-6P 158607-00-2P 158607-01-3P 158607-02-4P 158607-03-5P  
 158607-04-6P  
 RL: SPN (Synthetic preparation); PREP (Preparation)  
 (preparation of, as intermediate in preparation of lipoxygenase inhibitors)

IT 158606-72-5P 158606-73-6P 158606-74-7P 158606-75-8P 158606-76-9P  
 158606-77-0P 158606-78-1P 158606-79-2P 158606-80-5P  
 158606-81-6P 158606-82-7P 158606-83-8P 158606-84-9P  
 158606-85-0P 158606-86-1P 158606-87-2P 158606-88-3P  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (preparation of, as lipoxygenase inhibitor)

IT 623-51-8, Ethyl thioglycolate

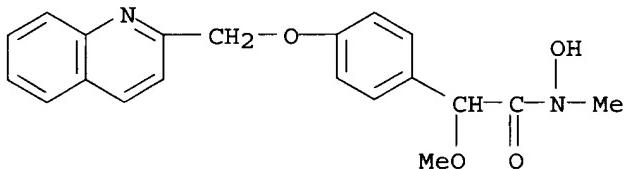
RL: RCT (Reactant); RACT (Reactant or reagent)  
 (thioetherification of, in preparation of (hetero)aryl-containing hydroxyamides  
 as lipoxygenase inhibitors)

IT 108-85-0, Cyclohexyl bromide 137-43-9, Bromocyclopentane 2404-35-5,  
 Cycloheptyl bromide 2550-36-9, (Bromomethyl)cyclohexane  
 RL: RCT (Reactant); RACT (Reactant or reagent)  
 ( $\alpha$ -alkylation by, in preparation of (hetero)aryl-containing hydroxyamides  
 as lipoxygenase inhibitors)

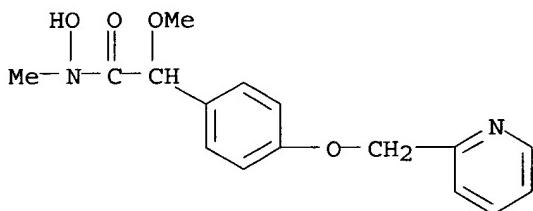
IT 158606-81-6P 158606-83-8P  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (preparation of, as lipoxygenase inhibitor)

RN 158606-81-6 HCPLUS

CN Benzeneacetamide, N-hydroxy- $\alpha$ -methoxy-N-methyl-4-(2-quinolinylmethoxy)- (9CI) (CA INDEX NAME)



RN 158606-83-8 HCPLUS  
 CN Benzeneacetamide, N-hydroxy- $\alpha$ -methoxy-N-methyl-4-(2-pyridinylmethoxy)- (9CI) (CA INDEX NAME)



L66 ANSWER 7 OF 26 HCPLUS COPYRIGHT 2005 ACS on STN  
 ACCESSION NUMBER: 1993:147306 HCPLUS  
 DOCUMENT NUMBER: 118:147306  
 TITLE: Preparation of  $\alpha$ -oxobenzeneacetic acids and related compounds as antiischemics and antiarrhythmics  
 INVENTOR(S): Guthrie, Robert William; Heathers, Guy Phillip;  
 Higgins, Alan John; Kachensky, David Francis;  
 Kierstead, Richard Wightmann; LeMahieu, Ronald Andrew;  
 Mullin, John Guilfoyle, Jr.; Tilley, Jefferson Wright  
 PATENT ASSIGNEE(S): Hoffmann-La Roche, F., AG, Switz.  
 SOURCE: Eur. Pat. Appl., 166 pp.  
 CODEN: EPXXDW  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 2  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 512352	A2	19921111	EP 1992-107135	19920427
EP 512352	A3	19930310		
EP 512352	B1	19960327		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, MC, NL, PT, SE US 5344843				
	A	19940906	US 1992-850620	19920313
PRIORITY APPLN. INFO.: )			US 1991-698014	A 19910509
			US 1992-850620	A 19920313

OTHER SOURCE(S): MARPAT 118:147306

ED Entered STN: 13 Apr 1993

AB Title compds. I [R1 = OH, OR3, NR4R5; 1 of R4, R5 = H, C1-7 (hydroxy)alkyl and the other = H, OH, C1-7 alkyl, C1-7 alkoxy; R3 = (CH<sub>2</sub>CH<sub>2</sub>O)<sub>m</sub>H, CH<sub>2</sub>CHOHCH<sub>2</sub>OH, 2,2-dimethyl-1,3-dioxolan-4-yl, CH<sub>2</sub>CH<sub>2</sub>NH<sub>2</sub>, etc.; m = 1-4; R2, R2' = H, C1-7 alkyl, aryl-C1-7 alkyl, C1-7 alkoxy, OH, NH<sub>2</sub>, C1-7 alkylamino, cyano, halo, SH, etc.; A = bond, O, NR<sub>7</sub>, S, SO, SO<sub>2</sub>, C.tplbond.C, CH:CH, CH<sub>2</sub>CH, NR<sub>8</sub>CO, CONR<sub>9</sub>; R7 = H, C1-7 alkyl, acyl; R8,R9 = H, C1-7 alkyl; n = 0-10; B = bond, groups defined for A, CO, CS, (OCH<sub>2</sub>CH<sub>2</sub>)<sub>m</sub>O, etc.; Z = O, S, CR<sub>2</sub>:CR<sub>2</sub>', N:CR<sub>2</sub>, CR<sub>2</sub>:N, NR<sub>11</sub>; R11 = H, C1-7 alkyl; XY = O, S, :NOH, alkoxyimino, alkenyloxyimino, hydrazone, etc., or individually 1 of X and Y = halo and the other = H, halo, C1-7 alkyl, aryl-C1-7 alkyl; other possibilities for X and Y; Q = cycloalkyl, aryl, heterocyclyl; with provisos] were prepared as drugs to prevent injury to ischemic tissue and arrhythmias during and after a myocardial infarction. Thus, Me 4-hydroxy- $\alpha$ -oxobenzeneacetate in DMF containing NaH was O-alkylated by Ph(CH<sub>2</sub>)<sub>3</sub>Br and the resultant product was hydrolyzed by NaOH in MeOH to give title compound II. II had IC<sub>50</sub> of 0.5  $\mu$ M against carnitine acyltransferase 1 in mitochondria. Over 200 I were prepared Capsules containing I were also prepared

IC ICM C07C059-90  
ICS A61K031-19; C07C065-40

CC 25-17 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)  
Section cross-reference(s): 1, 63

ST oxobenzeneacetic acid prepn antiischemic antiarrhythmic; myocardial infarction treatment oxobenzeneacetic acid

IT Ischemia  
(treatment of, oxobenzeneacetic acids and related compds. for)

IT Antiarrhythmics  
( $\alpha$ -oxobenzeneacetic acids and related compds.)

IT Heart, disease  
(infarction, treatment of, oxobenzeneacetic acids and related compds.  
for)

IT 39386-49-7  
RL: USES (Uses)  
(inhibitors,  $\alpha$ -oxobenzeneacetic acids and related compds.)

IT 145795-03-5P  
RL: SPN (Synthetic preparation); PREP (Preparation)  
(preparation of)

IT 145794-08-7P 145794-09-8P 145794-10-1P 145794-12-3P 145794-14-5P  
145794-16-7P 145794-20-3P 145794-21-4P 145794-23-6P 145794-25-8P  
145794-27-0P 145794-29-2P 145794-31-6P 145794-33-8P 145794-35-0P  
145794-37-2P 145794-39-4P 145794-41-8P 145794-43-0P 145794-45-2P  
145794-47-4P 145794-49-6P 145794-51-0P 145794-53-2P 145794-55-4P  
145794-57-6P 145794-59-8P 145794-61-2P 145794-63-4P 145794-65-6P  
145794-67-8P 145794-69-0P 145794-71-4P 145794-73-6P 145794-75-8P  
145794-77-0P 145794-79-2P 145794-80-5P 145794-82-7P 145794-84-9P  
145794-86-1P 145794-88-3P 145794-90-7P 145794-92-9P 145794-94-1P  
145794-96-3P 145794-98-5P 145794-99-6P 145795-01-3P 145795-02-4P  
145795-04-6P 145795-05-7P 145795-06-8P 145795-07-9P 145795-08-0P  
145795-09-1P 145795-10-4P 145795-11-5P 145795-12-6P 145795-13-7P

145795-14-8P	145795-15-9P	145795-16-0P	145795-17-1P	145795-18-2P
145795-19-3P	145795-20-6P	145795-21-7P	145795-22-8P	145795-23-9P
145795-24-0P	145795-25-1P	145795-26-2P	145795-27-3P	145795-28-4P
145795-29-5P	145795-30-8P	145795-31-9P	145795-32-0P	145795-33-1P
145795-34-2P	145795-35-3P	145795-36-4P	145795-37-5P	145795-38-6P
145795-39-7P	145795-40-0P	145795-41-1P	145795-42-2P	145795-43-3P
145795-44-4P	145795-45-5P	145795-46-6P	145795-47-7P	145795-48-8P
145795-49-9P	145795-50-2P	145795-51-3P	145795-52-4P	145795-53-5P
145795-54-6P	145795-55-7P	145795-56-8P	145795-57-9P	145795-58-0P
145795-59-1P	145795-60-4P	145795-61-5P	145795-62-6P	145795-63-7P
145795-64-8P	145795-65-9P	145795-66-0P	145795-67-1P	145795-68-2P
145795-69-3P	145795-70-6P	145795-71-7P	145795-72-8P	145795-73-9P
145795-74-0P	145795-75-1P	145795-76-2P	145795-77-3P	145795-78-4P
145795-79-5P	145795-80-8P	145795-81-9P	145795-82-0P	145795-83-1P
145795-84-2P	145795-85-3P	145795-86-4P	145795-87-5P	145795-88-6P
145795-89-7P	145795-90-0P	145795-91-1P	145795-92-2P	145795-93-3P
145795-94-4P	145795-95-5P	145795-96-6P	145795-97-7P	
145795-98-8P	145795-99-9P	145796-00-5P	145796-01-6P	145796-02-7P
145796-03-8P	145796-04-9P	145796-05-0P	145796-06-1P	145796-07-2P
145796-08-3P	145796-09-4P	145796-10-7P	145796-11-8P	145796-12-9P
145796-13-0P	145796-14-1P	145796-15-2P	145796-16-3P	145796-17-4P
145796-18-5P	145796-19-6P	145796-20-9P	145796-21-0P	145796-22-1P
145796-23-2P	145796-24-3P	145796-25-4P	145796-26-5P	145796-27-6P
145796-28-7P	145796-29-8P	145796-30-1P	145796-31-2P	145796-32-3P
145796-33-4P	145796-34-5P	145796-35-6P	145796-36-7P	145796-37-8P
145796-38-9P	145796-39-0P	145796-40-3P	145796-41-4P	145796-42-5P
145796-43-6P	145796-44-7P	145796-45-8P	145796-46-9P	145796-47-0P
145796-48-1P	145796-49-2P	145796-50-5P	145796-51-6P	145796-52-7P
145796-53-8P	145796-54-9P	145796-55-0P	145796-56-1P	145796-57-2P
145796-58-3P	145796-59-4P	145796-60-7P	145796-61-8P	145796-62-9P
145796-63-0P	145796-64-1P	145796-65-2P	145796-66-3P	145796-67-4P
145796-68-5P	145796-69-6P	145796-70-9P	145796-71-0P	145796-72-1P
145796-73-2P	145796-74-3P	146548-36-9P	146548-37-0P	146548-38-1P
146548-39-2P	146548-40-5P	146548-41-6P	146548-42-7P	146548-43-8P
146548-44-9P	146548-45-0P	146548-46-1P	146548-47-2P	146548-48-3P
146548-50-7P	146572-66-9P			

RL: SPN (Synthetic preparation); PREP (Preparation)

(preparation of, as antiischemic and antiarrhythmic)

IT	69651-48-5P	89012-04-4P	101125-34-2P	131003-09-3P	134748-95-1P
	145794-07-6P	145794-11-2P	145794-13-4P	145794-15-6P	145794-17-8P
	145794-18-9P	145794-19-0P	145794-22-5P	145794-24-7P	145794-26-9P
	145794-28-1P	145794-30-5P	145794-32-7P	145794-34-9P	145794-36-1P
	145794-38-3P	145794-40-7P	145794-42-9P	145794-44-1P	145794-46-3P
	145794-48-5P	145794-50-9P	145794-52-1P	145794-54-3P	145794-56-5P
	145794-58-7P	145794-60-1P	145794-62-3P	145794-64-5P	145794-66-7P
	145794-68-9P	145794-70-3P	145794-72-5P	145794-74-7P	145794-76-9P
	145794-78-1P	145794-81-6P	145794-83-8P	145794-85-0P	145794-87-2P
	145794-89-4P	145794-91-8P	145794-93-0P	145794-95-2P	145794-97-4P
	145795-00-2P	145795-29-5P	145795-31-9P	145796-75-4P	145796-76-5P
	145796-77-6P	145796-79-8P	145796-80-1P	145796-81-2P	145796-82-3P
	145796-83-4P	145796-84-5P	145796-85-6P	145796-86-7P	145796-87-8P
	145796-88-9P	145796-89-0P	145796-90-3P	145796-91-4P	145796-92-5P
	145796-93-6P	145796-94-7P	145796-95-8P	145796-96-9P	145796-97-0P
	145796-98-1P	145796-99-2P	145797-00-8P	145797-01-9P	145797-02-0P
	145797-03-1P	145797-04-2P	145797-05-3P	145797-06-4P	145797-07-5P
	145797-08-6P	145797-09-7P	145797-10-0P	145797-11-1P	145797-12-2P
	145797-13-3P	145797-14-4P	145797-15-5P	145797-16-6P	145797-17-7P
	145797-18-8P	145797-19-9P	145797-20-2P	145797-21-3P	145797-22-4P
	145797-23-5P	145797-24-6P	145797-25-7P	145797-26-8P	145797-27-9P
	145797-28-0P	145797-29-1P	145797-30-4P	145797-31-5P	145797-32-6P

145797-33-7P	145797-34-8P	145797-35-9P	145797-36-0P	145797-37-1P
145797-38-2P	145797-39-3P	145797-40-6P	145797-41-7P	145797-42-8P
145797-43-9P	145797-44-0P	145797-45-1P	145797-46-2P	145797-47-3P
145797-48-4P	145797-49-5P	145797-50-8P	145797-51-9P	145797-52-0P
145797-53-1P	145797-54-2P	145797-55-3P	145797-56-4P	145797-57-5P
145797-58-6P	145797-59-7P	145797-60-0P	145797-61-1P	145797-62-2P
145797-63-3P	145797-64-4P	145797-65-5P	145797-66-6P	145797-67-7P
145797-68-8P	145797-69-9P	145797-70-2P	145797-71-3P	145797-72-4P
145797-73-5P	145797-74-6P	145797-75-7P	145797-76-8P	145797-77-9P
145797-78-0P	145797-79-1P	145797-80-4P	145797-81-5P	145797-82-6P
145797-83-7P	145797-84-8P	145797-85-9P	145797-86-0P	145797-87-1P
145797-88-2P	145797-89-3P	145797-90-6P	145797-91-7P	145797-92-8P
145797-93-9P	145797-94-0P	145797-95-1P	145797-96-2P	145797-97-3P
145797-98-4P	145797-99-5P	145798-00-1P	145798-01-2P	145798-02-3P
145798-03-4P	145798-04-5P	145798-05-6P	145798-06-7P	145798-07-8P
145798-08-9P	145798-09-0P	145798-10-3P	145798-11-4P	145798-12-5P
145798-13-6P	145798-14-7P	145798-15-8P	145798-16-9P	145798-17-0P
145798-18-1P	145798-19-2P	145798-20-5P	145798-21-6P	145798-22-7P
145798-23-8P	145798-24-9P	145798-25-0P	145798-26-1P	145798-27-2P
145798-28-3P	146572-67-0P	160062-32-8P		

RL: SPN (Synthetic preparation); PREP (Preparation)  
(preparation of, as intermediate for antiischemics and antiarrhythmics)

IT 56-81-5, Glycerol, reactions 74-88-4, Methyl iodide, reactions  
75-16-1, Methyl magnesium bromide 75-36-5, Acetyl chloride 79-22-1,  
Methyl chloroformate 91-21-4, 1,2,3,4-Tetrahydroisoquinoline 92-44-4,  
2,3-Dihydroxynaphthalene 93-20-9 96-49-1, Ethylene carbonate  
100-39-0, Benzyl bromide 100-79-8, Solketal 106-89-8, Epichlorohydrin,  
reactions 108-00-9, N,N-Dimethylethylenediamine 108-01-0 108-95-2,  
Phenol, reactions 109-86-4 111-42-2, Diethanolamine, reactions  
112-27-6, Triethylene glycol 122-99-6, 2-Phenoxyethanol 124-40-3,  
Dimethylamine, reactions 124-63-0, Methanesulfonyl chloride 141-43-5,  
Ethanolamine, reactions 358-23-6, Triflic anhydride 403-14-5  
460-00-4, 4-Fluorobromobenzene 544-92-3, Cuprous cyanide 563-41-7,  
Semicarbazide hydrochloride 588-63-6 589-10-6,  $\beta$ -Bromophenetole  
593-56-6, Methoxylamine hydrochloride 593-77-1, N-Methylhydroxylamine  
613-54-7, Bromomethyl 2-naphthyl ketone 637-59-2, 3-Bromo-1-  
phenylpropane 691-64-5 769-39-1, 2,3,5,6-Tetrafluorophenol 875-59-2  
876-02-8 920-39-8, Isopropylmagnesium bromide 939-26-4,  
2-Bromomethylnaphthalene 1137-41-3, p-Aminobenzophenone 1200-03-9  
1590-22-3 1817-88-5 1940-28-9, 4-Bromo-3,5-dichlorophenol 2243-83-6,  
2-Naphthoyl chloride 2450-71-7, Propargylamine 2478-38-8 2605-67-6  
2687-43-6, O-Benzylhydroxylamine hydrochloride 2892-29-7 2967-54-6,  
3,5-Difluoro-4-hydroxybenzonitrile 3332-29-4 3355-31-5 3747-74-8,  
2-Chloromethylquinoline hydrochloride 3814-20-8 4225-92-7 4755-77-5  
5856-77-9, 2,2-Dimethylbutyryl chloride 6089-04-9 6315-52-2  
6322-56-1 6707-01-3, Chloromethoxybenzene 13246-14-5 15573-67-8  
16839-97-7, 2-Methoxythiophene 17044-70-1 18162-48-6,  
tert-Butyldimethylsilyl chloride 20009-28-3 2020-27-3 21087-29-6  
21886-62-4 22118-09-8, Bromoacetyl chloride 22921-72-8 23287-26-5  
23314-24-1 24484-55-7 27650-59-5 31076-84-3, 4-Acetylbenzoyl  
chloride 32462-30-9 34604-52-9 36754-60-6, 2-Chloromethylbenzofuran  
37595-74-7 38250-16-7 38945-21-0 39199-93-4 40299-87-4  
40786-20-7 40926-77-0 41656-75-1 51795-97-2 53542-78-2  
54537-30-3 60753-14-2, 3-Pyridinebutanol 61236-14-4 62001-72-3  
63649-88-7 63649-90-1 63650-21-5 64957-86-4 65512-08-5  
66340-55-4 68301-59-7 69189-03-3 76469-33-5 77923-27-4  
86902-13-8 87271-22-5 87723-22-6 91540-82-8 93957-49-4  
98619-07-9 98793-02-3 99690-59-2 110754-02-4 113272-40-5  
120895-36-5 123843-57-2 128988-59-0 132464-59-6 134472-49-4  
141929-43-3 145794-38-3 145794-87-2 145798-29-4 145798-30-7

145798-31-8	145798-32-9	145798-33-0	145798-34-1	145798-35-2
145798-36-3	145798-37-4	145798-38-5	145798-39-6	145798-40-9
145798-41-0	145798-42-1	145798-43-2	145798-44-3	145798-45-4
145798-46-5	145798-47-6	145798-48-7	145798-49-8	145798-50-1
145798-51-2	145798-52-3	145798-53-4	145798-54-5	145798-55-6
145798-56-7	145798-57-8	145798-58-9	145798-59-0	145798-60-3
145798-61-4	145798-62-5	145798-63-6	145798-64-7	145798-65-8

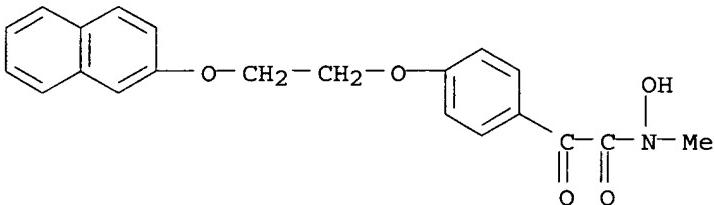
RL: RCT (Reactant); RACT (Reactant or reagent)  
(reaction of, in preparation of antiischemics and antiarrhythmics)

IT 145795-96-6P

RL: SPN (Synthetic preparation); PREP (Preparation)  
(preparation of, as antiischemic and antiarrhythmic)

RN 145795-96-6 HCPLUS

CN Benzeneacetamide, N-hydroxy-N-methyl-4-[2-(2-naphthalenylloxy)ethoxy]-  
α-oxo- (9CI) (CA INDEX NAME)



L66 ANSWER 8 OF 26 HCPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1992:611677 HCPLUS

DOCUMENT NUMBER: 117:211677

TITLE: Synthesis, chemical, and biological properties of vinylogous hydroxamic acids: dual inhibitors of 5-lipoxygenase and IL-1 biosynthesis

AUTHOR(S): Wright, Stephen W.; Harris, Richard R.; Kerr, Janet S.; Green, Alicia M.; Pinto, Donald J.; Bruin, Elaine M.; Collins, Robert J.; Dorow, Roberta L.; Mantegna, Lisa R.; et al.

CORPORATE SOURCE: Inflammatory Dis. Res., Du Pont Merck Pharm. Co., Wilmington, DE, 19880-0353, USA

SOURCE: Journal of Medicinal Chemistry (1992), 35(22), 4061-8  
CODEN: JMCMAR; ISSN: 0022-2623

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 117:211677

ED Entered STN: 28 Nov 1992

AB Vinylogous hydroxamic acids, 3-(N-hydroxy-N-alkylamino)-2-propen-1-ones (VHAs), were prepared as antiinflammatory agents. The synthesis, chemical properties, and in vitro biol. activities of these relatively unexplored compds. are described. The VHAs were prepared by condensation of the appropriate N-substituted hydroxylamine with any of three reagents: a 1,3-dicarbonyl compound, a vinylogous amide, or an alkynone. The VHAs exist as one or more tautomers in solution with the relative proportions of each being dependent upon the structure of the VHA, solvent, and pH. VHAs undergo some of the typical reactions of hydroxamic acids as well as those of vinylogous amides. VHAs are active as inhibitors of 5-lipoxygenase and of IL-1 biosynthesis in vitro, which do not inhibit other enzymes of the arachidonic acid cascade. They have been shown by ESR studies to bring about inhibition of soybean type 1 15-lipoxygenase by reduction of the active site iron.

CC 21-2 (General Organic Chemistry)  
 Section cross-reference(s): 1

ST vinylogous hydroxamic acid prepn antiinflammatory; lipoxygenase inhibition  
 vinylogous hydroxamic acid; Ill biosynthesis inhibition vinylogous  
 hydroxamic acid; tautomer vinylogous hydroxamic acid

IT Tautomerism and Tautomers  
 (of vinylogous hydroxamic acids)

IT Inflammation inhibitors  
 (vinylogous hydroxamic acids)

IT Lymphokines and Cytokines  
 RL: RCT (Reactant); RACT (Reactant or reagent)  
 (interleukin 1 $\beta$ , inhibition of biosynthesis of, by vinylogous  
 hydroxamic acids)

IT 403-42-9  
 RL: RCT (Reactant); RACT (Reactant or reagent)  
 (acylation of)

IT 88-15-3, 2-Acetylthiophene 100-06-1 100-19-6 120-44-5,  
 1,2-Di-p-anisylethanone 451-40-1, 1,2-Diphenylethanone 765-43-5,  
 Acetylcyclopropane 1122-54-9, 4-Acetylpyridine 1192-62-7,  
 2-Acetyl furan 1468-83-3, 3-Acetylthiophene 4495-66-3 22720-75-8  
 30071-93-3 54696-05-8, 4-Benzylxyacetophenone 87483-29-2  
 143620-85-3  
 RL: RCT (Reactant); RACT (Reactant or reagent)  
 (condensation of, with DMF acetal)

IT 4637-24-5, Dimethylformamide dimethyl acetal  
 RL: RCT (Reactant); RACT (Reactant or reagent)  
 (condensation of, with acetyl furan)

IT 67860-32-6  
 RL: RCT (Reactant); RACT (Reactant or reagent)  
 (condensation of, with benzylhydroxylamine)

IT 100-65-2, N-Phenylhydroxylamine 593-77-1, N-Methylhydroxylamine  
 622-30-0, N-Benzylhydroxylamine 2211-64-5, N-Cyclohexylhydroxylamine  
 3217-93-4 7803-49-8, Hydroxylamine, reactions 134796-86-4  
 143620-84-2  
 RL: RCT (Reactant); RACT (Reactant or reagent)  
 (condensation of, with propanedione derivative)

IT 26228-72-8, N-Decylhydroxylamine 106328-99-8 111525-02-1 143620-86-4  
 RL: RCT (Reactant); RACT (Reactant or reagent)  
 (condensation of, with propenone derivative)

IT 623-91-6, Diethyl fumarate 941-69-5, N-Phenylmaleimide  
 RL: RCT (Reactant); RACT (Reactant or reagent)  
 (cycloaddn. reaction of, with hydroxylaminopropenone derivative)

IT 99-91-2  
 RL: RCT (Reactant); RACT (Reactant or reagent)  
 (formylation and condensation of, with DMF acetal)

IT 93-08-3  
 RL: RCT (Reactant); RACT (Reactant or reagent)  
 (formylation and reaction with hydroxylamine derivative)

IT 75-97-8, tert-Butyl methyl ketone 92-91-1 529-34-0, 1-Tetralone  
 579-74-8 2040-05-3 2642-63-9  
 RL: RCT (Reactant); RACT (Reactant or reagent)  
 (formylation of)

IT 9029-60-1  
 RL: PROC (Process)  
 (inhibition of, by vinylogous hydroxamic acids)

IT 143620-64-8P 143620-65-9P 143620-67-1P 143620-73-9P 143620-89-7P  
 143620-90-0P 143621-01-6P 143621-02-7P 143621-03-8P 143621-04-9P  
 143621-08-3P 143621-09-4P 143621-10-7P 143621-12-9P 143621-13-0P  
 143621-14-1P 143621-16-3P 143621-17-4P 143621-19-6P 143621-20-9P  
 143621-21-0P 143621-22-1P 143621-23-2P 143621-24-3P 143621-25-4P

143621-26-5P 143621-30-1P 143631-85-0P 143631-86-1P  
 RL: SPN (Synthetic preparation); PREP (Preparation)  
 (preparation and inhibition by, of 5-lipoxygenase and IL-1 biosynthesis)

IT 143620-66-0P 143620-68-2P 143620-69-3P 143620-70-6P 143620-71-7P  
 143620-72-8P 143620-74-0P 143620-75-1P 143620-76-2P 143620-91-1P  
 143620-92-2P 143620-94-4P 143620-95-5P 143620-96-6P 143620-97-7P  
 143620-98-8P 143620-99-9P 143621-00-5P 143621-05-0P 143621-06-1P  
 143621-07-2P 143621-11-8P 143621-15-2P 143621-18-5P 143621-27-6P  
 143621-28-7P 143621-29-8P 143631-83-8P 143631-87-2P  
 RL: SPN (Synthetic preparation); PREP (Preparation)  
 (preparation and inhibition of 5'-lipoxygenase by)

IT 56856-73-6P  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT  
 (Reactant or reagent)  
 (preparation and reaction of, with benzylhydroxylamine)

IT 109482-86-2P  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT  
 (Reactant or reagent)  
 (preparation and reaction of, with hydroxylamine derivative)

IT 143620-77-3P 143620-78-4P 143620-79-5P 143620-80-8P 143620-81-9P  
 143620-82-0P 143620-83-1P 143631-84-9P  
 RL: SPN (Synthetic preparation); PREP (Preparation)  
 (preparation of)

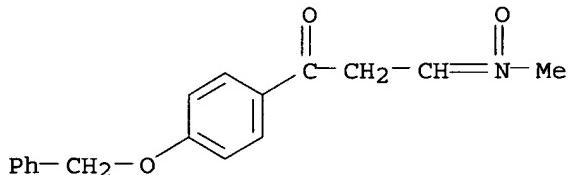
IT 143620-93-3P  
 RL: SPN (Synthetic preparation); PREP (Preparation)  
 (preparation, reactions, tautomerism, and inhibition by, of 5'-lipoxygenase  
 and IL-1 biosynthesis)

IT 142556-94-3P 143620-87-5P 143620-88-6P  
 RL: SPN (Synthetic preparation); PREP (Preparation)  
 (preparation, tautomerism, and inhibition by, of 5'-lipoxygenase and IL-1  
 biosynthesis)

IT 922-67-8, Methyl propiolate  
 RL: RCT (Reactant); RACT (Reactant or reagent)  
 (reaction of, with benzyloxybenzylhydroxylamine)

IT 143620-87-5P  
 RL: SPN (Synthetic preparation); PREP (Preparation)  
 (preparation, tautomerism, and inhibition by, of 5'-lipoxygenase and IL-1  
 biosynthesis)

RN 143620-87-5 HCPLUS  
 CN 1-Propanone, 3-(methyloxidoimino)-1-[4-(phenylmethoxy)phenyl]- (9CI) (CA  
 INDEX NAME)



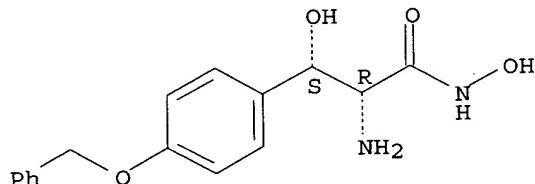
L66 ANSWER 9 OF 26 HCPLUS COPYRIGHT 2005 ACS on STN  
 ACCESSION NUMBER: 1968:12886 HCPLUS  
 DOCUMENT NUMBER: 68:12886  
 TITLE: Synthesis of trans-5-(p-hydroxyphenyl)-4-amino-3-isoxazolidone as an inhibitor of enzymic conversions involving tyrosine  
 AUTHOR(S): Khomutov, R. M.; Severin, E. S.; Gulyaev, N. N.

CORPORATE SOURCE: Inst. Molek. Biol., Moscow, USSR  
 SOURCE: Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya  
 (1967), (7), 1622-4  
 CODEN: IASKA6; ISSN: 0002-3353

DOCUMENT TYPE: Journal  
 LANGUAGE: Russian

ED Entered STN: 12 May 1984  
 AB Threo- $\beta$ -p-benzyloxyphenylserine and 1 mole HCl in MeOH cooled to 0° and kept overnight gave the Me ester HCl, m. 165-6°, which treated with MeONa in MeOH, then with HONH<sub>2</sub> solution in MeOH at -5°, then 20° overnight, gave 66% p-PhCH<sub>2</sub>OC<sub>6</sub>H<sub>4</sub>CH(OH)CH(NH<sub>2</sub>)CONHOH, threo isomer, decomposed 150-1°, which hydrogenated over Pd to 80% p-hydrogenated analog, decomposed 155-6°. This in the presence of concentrated H<sub>2</sub>SO<sub>4</sub> at -15° formed trans-5-p-hydroxyphenyl-4-amino-3-isoxazolidone, 26%, decomposed 135-40°. The substance is an inhibitor of enzymic changes of tyrosine.  
 CC 28 (Heterocyclic Compounds (More Than One Hetero Atom))  
 ST INHIBITOR ENZYMIC CHANGES TYROSINE; ISOXALIDONES AMINO; AMINO ISOXALIDONES; TYROSINE ENZYMIC CHANGES INHIBITOR  
 IT 60-18-4, biological studies  
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)  
 (metabolism of, inhibition by trans-4-amino-5-(p-hydroxyphenyl)-3-isoxazolidinone)  
 IT 16444-07-8P 16444-08-9P 16446-49-4P 16446-50-7P  
 RL: SPN (Synthetic preparation); PREP (Preparation)  
 (preparation of)  
 IT 16444-07-8P  
 RL: SPN (Synthetic preparation); PREP (Preparation)  
 (preparation of)  
 RN 16444-07-8 HCPLUS  
 CN Hydracyclohydroxamic acid, 2-amino-3-[p-(benzyloxy)phenyl]-, threo- (8CI)  
 (CA INDEX NAME)

Relative stereochemistry.



L66 ~ ANSWER 10 OF 26 HCPLUS COPYRIGHT 2005 ACS on STN  
 ACCESSION NUMBER: 1945:1769 HCPLUS  
 DOCUMENT NUMBER: 39:1769  
 ORIGINAL REFERENCE NO.: 39:286a-g  
 TITLE: Synthetic norephedrine and isoquinoline derivatives  
 AUTHOR(S): v. Fodor, Gabor  
 SOURCE: Ber. (1943), 76B, 1216-23  
 DOCUMENT TYPE: Journal  
 LANGUAGE: Unavailable  
 OTHER SOURCE(S): CASREACT 39:1769  
 ED Entered STN: 16 Dec 2001  
 AB cf. C. A. 38, 2045.7. Eugenol (200 g.) in 600 cc. EtOH, treated with 70 g. KOH in 70 cc. H<sub>2</sub>O and then with 160 g. PhCH<sub>2</sub>Cl, shaken at 20°

and finally heated 2 h. at 100°, gives eugenol benzyl ether; solution in 1.3 l. EtOH, addition of 500 g. powdered KOH and heating 17-20 h. give 84% of

isoeugenol benzyl ether (I). I results in 91% yield from 100 g. isoeugenol in 300 cc. EtOH, 35 g. KOH in 50 cc. H<sub>2</sub>O and 80 g. PhCH<sub>2</sub>Cl on boiling 3.5 h. I (100 g.) in 1 l. ether and 280 g. NaNO<sub>2</sub> in 150 cc. H<sub>2</sub>O, treated during 5-6 h. with 1 l. 20% H<sub>2</sub>SO<sub>4</sub> and allowed to stand overnight, give 77% of the  $\psi$ -nitrosite (II), m. 125-6° (decomposition). A suspension of 33 g. II in 90 cc. H<sub>2</sub>O at 8-10°, treated with 2 drops concentrated H<sub>2</sub>SO<sub>4</sub> (temperature not above 20°), stirred for 15 min. and poured into 1 l. H<sub>2</sub>O, gives 80% of 1-(3-methoxy-4-benzyloxyphenyl)-1-acetoxy-2-nitropropane (III), m. 130°. II or III with KOH in 75% EtOH gives  $\beta$ -nitroisoeugenol benzyl ether, canary-yellow, m. 92°. Reduction of 14.5 g. III in 100 cc. AcOH and 200 cc. EtOH at 50-60° with a Pb cathode (0.07 amp./sq. cm.), 10 cc. concentrated HCl being added during the reduction, gives 32% of 1-(3-methoxy-4-benzyloxyphenyl)-1-hydroxy-2-acetamidopropane (IV), m. 138° (purified by extraction of the AcOEt solution with N NaOH), and 38% of 1-(3-methoxy-4-benzyloxyphenyl)-1-hydroxy-2-(N-acetylhydroxyamino)propane (V), m. 144-7°; V reduces Fehling solution at room temperature and gives a deep violet color with FeCl<sub>3</sub>.

Reduction of

III in AcOH-EtOH with a Hg cathode for 1.5 h. gives 60% of IV. IV (1.65 g.) and 1.1 cc. 5 N EtOH-HCl, heated at 30-40°, gives 1.5 g. of 1-(3-methoxy-4-benzyloxyphenyl)-1-acetoxy-2-aminopropane-HCl (VI), m. 193°; 1 g. V in 20 cc. H<sub>2</sub>O and 4 cc. N NaOH gives 0.41 g. of IV. IV (4.82 g.) in 29 cc. N HCl and 18 cc. H<sub>2</sub>O, heated 3 h. on the water bath and treated dropwise with 43 cc. N NaOH, gives 42% of 1-(3-methoxy-4-benzyloxyphenyl)-1-hydroxy-2-aminopropane[3-methoxy-4-benzyloxynorephedrine] (VII), m. 129°; HCl salt (VIII), m. 210°. VIII also results in 3.2-g. yield by treating 6.58 g. of IV in 20 cc. EtOH with 4.8 cc. 4.2 N EtOH-HCl and then with 35 cc. H<sub>2</sub>O and refluxing 6 h. VII (1.15 g.) in 20 cc. MeOH, shaken with H (Pd-charcoal) for 10 min., gives 0.8 g. of 3-methoxy-4-hydroxynorephedrine (IX), m. 149-50°; 2.5 g. VIII similarly gives 1.66 g. of the HCl salt of IX, m. 206°. IX and CH<sub>2</sub>N<sub>2</sub> give 1-(3,4-dimethoxyphenyl)-2-amino-1-propanol, m. 126-8° (Pfeiffer, C. A. 34, 2383.3). V (0.7 g.) in 10 cc. EtOH and 1 cc. 6 N EtOH-HCl, allowed to stand 2 h., gives 0.57 g. of 1-(3-methoxy-4-benzyloxyphenyl)-1-acetoxy-2-hydroxy-aminopropane-HCl, m. 163°; with alkali this yields VI. IV (1.65 g.) in 17 cc. CHCl<sub>3</sub> and 1.5 cc. POCl<sub>3</sub>, refluxed 3 h., gives 69% of 1,3-dimethyl-6-methoxy-7-benzyloxy-isouquinoline (X), m. 150°; HCl salt, m. 245°; nitrate, m. 215° (decomposition). Catalytic reduction of X in PhMeEtOH at room temperature gives 1,3-dimethyl-6-methoxy-7-hydroxyisouquinoline (XI), m. 175°; HCl salt, m. 265° (decomposition); CH<sub>2</sub>N<sub>2</sub> gives the 6,7-di-MeO derivative, m. 119-20°. XI and 3,4-(MeO)<sub>2</sub>C<sub>6</sub>H<sub>3</sub>CH<sub>2</sub>Cl with aqueous KOH in EtOH give 33% of 1,3-dimethyl-6-methoxy-7-(3,4-dimethoxybenzyloxy)isouquinoline, m. 180-1°.

CC 10 (Organic Chemistry)

IT 7-Isoquinolinol, 6-methoxy-1,3-dimethyl-Acetamide, N-[4-(benzyloxy)- $\beta$ -hydroxy-3-methoxy- $\alpha$ -methylphenethyl]-

Hydroxylamine, N-[4-(benzyloxy)- $\beta$ -hydroxy-3-methoxy- $\alpha$ -methylphenethyl]-, acetate-HCl

Norephedrine, 4-(benzyloxy)-N-hydroxy-3-methoxy-,  $\alpha$ -acetate-HCl

Norephedrine, 4-hydroxy-3-methoxy-

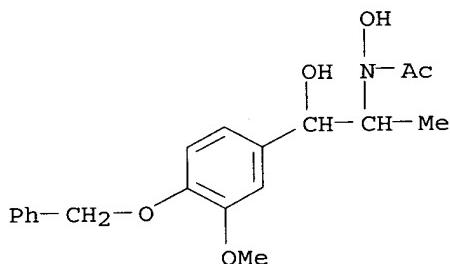
Norephedrine, 4-hydroxy-3-methoxy-, -HCl

Norephedrine, N-acetyl-4-(benzyloxy)-3-methoxy-

Norephedrine, N-acetyl-4-(benzyloxy)-N-hydroxy-3-methoxy-

IT Norephedrine, 4-(benzyloxy)-3-methoxy-  
(and derivs.)

IT Isoquinoline, 7-(benzyloxy)-6-methoxy-1,3-dimethyl-  
(and salts)  
IT 119-65-3, Isoquinoline 14838-15-4, Norephedrine  
(derivs.)  
IT 120-11-6, Benzene, 1-(benzyloxy)-2-methoxy-4-propenyl- 57371-42-3,  
Benzene, 4-allyl-1-(benzyloxy)-2-methoxy- 321125-48-8, Benzene,  
1-(benzyloxy)-2-methoxy-4-(2-nitropropenyl)- 749873-38-9, Benzene,  
1-(benzyloxy)-2-methoxy-4-(2-nitro-1-nitrosopropyl)- 850857-65-7,  
7-Isoquinolinol, 6-methoxy-1,3-dimethyl-, -HCl 850858-37-6,  
Isoquinoline, 6-methoxy-1,3-dimethyl-7-veratryloxy- 855273-11-9, Benzyl  
alcohol, 4-(benzyloxy)-3-methoxy- $\alpha$ -1-nitroethyl-, acetate  
855273-17-5, Benzyl alcohol, 4-(benzyloxy)- $\alpha$ -(1-hydroxaminoethyl)-3-  
methoxy-,  $\alpha$ -acetate-HCl 855883-23-7, Hydroxylamine,  
N-acetyl-N-[4-(benzyloxy)- $\beta$ -hydroxy-3-methoxy- $\alpha$ -  
methylphenethyl]- 855883-23-7, Acetamide, N-[4-(benzyloxy)-  
 $\beta$ -hydroxy-3-methoxy- $\alpha$ -methylphenethyl]-N-hydroxy-  
(preparation of)  
IT 855883-23-7, Hydroxylamine, N-acetyl-N-[4-(benzyloxy)- $\beta$ -  
hydroxy-3-methoxy- $\alpha$ -methylphenethyl]-  
(preparation of)  
RN 855883-23-7 HCPLUS  
CN Acetamide, N-[4-(benzyloxy)- $\beta$ -hydroxy-3-methoxy- $\alpha$ -  
methylphenethyl]-N-hydroxy- (4CI) (CA INDEX NAME)



=> d ibib ab hitstr 166 11-22  
YOU HAVE REQUESTED DATA FROM FILE 'HCPLUS, USPATFULL, BEILSTEIN, CHEMCATS' -  
CONTINUE? (Y)/N:y

L66 ANSWER 11 OF 26 USPATFULL on STN DUPLICATE 2  
ACCESSION NUMBER: 2004:300230 USPATFULL  
TITLE: Compounds for the treatment of metabolic disorders  
INVENTOR(S): Sharma, Shalini, Gaithersburg, MD, UNITED STATES  
Borstel, Reid W. von, Potomac, MD, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004236100	A1	20041125
	US 6858602	B2	20050222
APPLICATION INFO.:	US 2003-684660	A1	20031014 (10)
RELATED APPLN. INFO.:	Division of Ser. No. US 2002-167839, filed on 12 Jun 2002, PENDING		

NUMBER	DATE
--------	------

PRIORITY INFORMATION: US 2001-297282P 20010612 (60)  
 DOCUMENT TYPE: Utility  
 FILE SEGMENT: APPLICATION  
 LEGAL REPRESENTATIVE: LEWIS J. KREISLER, LEGAL DEPARTMENT, 930 CLOPPER ROAD,  
 GAITHERSBURG, MD, 20878

NUMBER OF CLAIMS: 9  
 EXEMPLARY CLAIM: 1  
 NUMBER OF DRAWINGS: 2 Drawing Page(s)  
 LINE COUNT: 4283

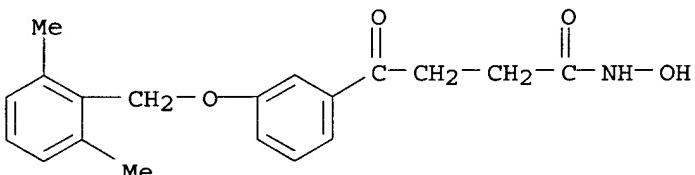
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Compounds useful for the treatment of various metabolic disorders, such as insulin resistance syndrome, diabetes, hyperlipidemia, fatty liver disease, cachexia, obesity, atherosclerosis and arteriosclerosis, are disclosed.

IT 478162-92-4P (preparation of benzyloxyphenyloxobutyrate and related compds. for treatment of metabolic disorders)

RN 478162-92-4 USPATFULL

CN Benzenebutanamide, 3-[(2,6-dimethylphenyl)methoxy]-N-hydroxy- $\gamma$ -oxo- (9CI) (CA INDEX NAME)



L66 ANSWER 12 OF 26 USPATFULL on STN DUPLICATE 3  
 ACCESSION NUMBER: 2004:127601 USPATFULL  
 TITLE: Compounds for the treatment of metabolic disorders  
 INVENTOR(S): Sharma, Shalini, Gaithersburg, MD, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004097585	A1	20040520
	US 6916848	B2	20050712
APPLICATION INFO.:	US 2003-684730	A1	20031014 (10)
RELATED APPLN. INFO.:	Division of Ser. No. US 2002-167839, filed on 12 Jun 2002, PENDING		

	NUMBER	DATE
PRIORITY INFORMATION:	US 2001-297282P	20010612 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	LEWIS J. KREISLER, LEGAL DEPARTMENT, 930 CLOPPER ROAD, GAITHERSBURG, MD, 20878	
NUMBER OF CLAIMS:	3	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	2 Drawing Page(s)	
LINE COUNT:	4236	
CAS INDEXING IS AVAILABLE FOR THIS PATENT.		
AB	Compounds useful for the treatment of various metabolic disorders, such as insulin resistance syndrome, diabetes, hyperlipidemia, fatty liver	

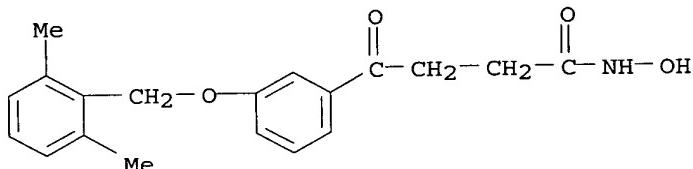
disease, cachexia, obesity, atherosclerosis and arteriosclerosis, are disclosed.

IT 478162-92-4P

(preparation of benzyloxyphenyloxobutyrates and related compds. for treatment of metabolic disorders)

RN 478162-92-4 USPATFULL

CN Benzenebutanamide, 3-[(2,6-dimethylphenyl)methoxy]-N-hydroxy- $\gamma$ -oxo- (9CI) (CA INDEX NAME)



L66 ANSWER 13 OF 26 USPATFULL on STN

DUPLICATE 4

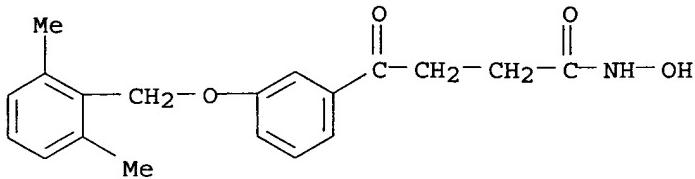
ACCESSION NUMBER: 2004:121100 USPATFULL

TITLE: Compounds for the treatment of metabolic disorders

INVENTOR(S): Sharma, Shalini, Gaithersburg, MD, UNITED STATES

von Borstel, Reid W., Potomac, MD, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004092516	A1	20040513
	US 6946491	B2	20050920
APPLICATION INFO.:	US 2003-685183	A1	20031014 (10)
RELATED APPLN. INFO.:	Division of Ser. No. US 2002-167839, filed on 12 Jun 2002, PENDING		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		
LEGAL REPRESENTATIVE:	LEWIS J. KREISLER, LEGAL DEPARTMENT, 930 CLOPPER ROAD, GAITHERSBURG, MD, 20878		
NUMBER OF CLAIMS:	21		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	2 Drawing Page(s)		
LINE COUNT:	4396		
CAS INDEXING IS AVAILABLE FOR THIS PATENT.			
AB	Compounds useful for the treatment of various metabolic disorders, such as insulin resistance syndrome, diabetes, hyperlipidemia, fatty liver disease, cachexia, obesity, atherosclerosis and arteriosclerosis, are disclosed.		
IT 478162-92-4P	(preparation of benzyloxyphenyloxobutyrates and related compds. for treatment of metabolic disorders)		
RN 478162-92-4 USPATFULL			
CN Benzenebutanamide, 3-[(2,6-dimethylphenyl)methoxy]-N-hydroxy- $\gamma$ -oxo- (9CI) (CA INDEX NAME)			



L66 ANSWER 14 OF 26 USPATFULL on STN DUPLICATE 5  
 ACCESSION NUMBER: 2004:102026 USPATFULL  
 TITLE: Compounds for the treatment of metabolic disorders  
 INVENTOR(S): Sharma, Shalini, Gaithersburg, MD, UNITED STATES  
 von Borstel, Reid W., Potomac, MD, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004077896	A1	20040422
	US 6924314	B2	20050802
APPLICATION INFO.:	US 2003-684644	A1	20031014 (10)
RELATED APPLN. INFO.:	Division of Ser. No. US 2002-167839, filed on 12 Jun 2002, PENDING		

	NUMBER	DATE
PRIORITY INFORMATION:	US 2001-297282P	20010612 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	LEWIS J. KREISLER, LEGAL DEPARTMENT, 930 CLOPPER ROAD, GAITHERSBURG, MD, 20878	
NUMBER OF CLAIMS:	13	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	2 Drawing Page(s)	
LINE COUNT:	4276	

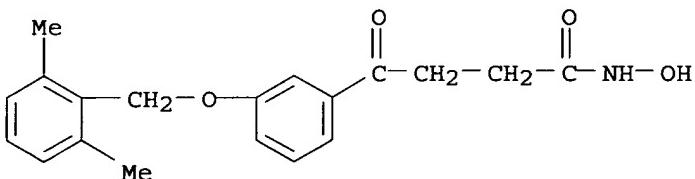
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Compounds useful for the treatment of various metabolic disorders, such as insulin resistance syndrome, diabetes, hyperlipidemia, fatty liver disease, cachexia, obesity, atherosclerosis and arteriosclerosis, are disclosed.

IT 478162-92-4P  
 (preparation of benzyloxyphenyloxobutyrates and related compds. for treatment of metabolic disorders)

RN 478162-92-4 USPATFULL

CN Benzenebutanamide, 3-[(2,6-dimethylphenyl)methoxy]-N-hydroxy-gamma-oxo- (9CI) (CA INDEX NAME)

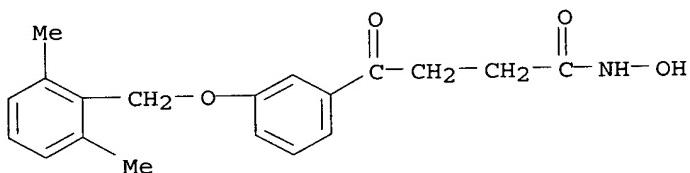


L66 ANSWER 15 OF 26 USPATFULL on STN

ACCESSION NUMBER: 2005:105617 USPATFULL  
 TITLE: Compound for the treatment of metabolic disorders  
 INVENTOR(S): Sharma, Shalini, Gaithersburg, MD, UNITED STATES  
 von Borstel, Reid W., Potomac, MD, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2005090555	A1	20050428
APPLICATION INFO.:	US 2004-5449	A1	20041206 (11)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 2004-865088, filed on 10 Jun 2004, ABANDONED Continuation of Ser. No. US 2002-167839, filed on 12 Jun 2002, PENDING		

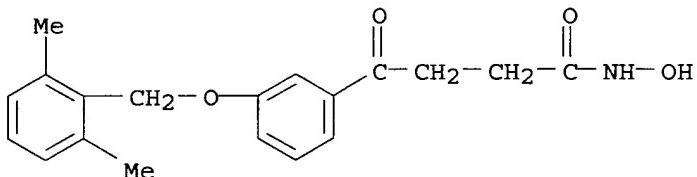
	NUMBER	DATE
PRIORITY INFORMATION:	US 2001-297282P	20010612 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	LEWIS J. KREISLER, LEGAL DEPARTMENT, 930 CLOPPER ROAD, GAITHERSBURG, MD, 20878, US	
NUMBER OF CLAIMS:	44	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	2 Drawing Page(s)	
LINE COUNT:	4271	
CAS INDEXING IS AVAILABLE FOR THIS PATENT.		
AB	Compounds useful for the treatment of various metabolic disorders, such as insulin resistance syndrome, diabetes, hyperlipidemia, fatty liver disease, cachexia, obesity, atherosclerosis and arteriosclerosis, are disclosed.	
IT	<b>478162-92-4P</b> (preparation of benzyloxyphenyloxobutyrates and related compds. for treatment of metabolic disorders)	
RN	478162-92-4 USPATFULL	
CN	Benzenebutanamide, 3-[(2,6-dimethylphenyl)methoxy]-N-hydroxy- $\gamma$ -oxo- (9CI) (CA INDEX NAME)	



L66 ANSWER 16 OF 26 USPATFULL on STN  
 ACCESSION NUMBER: 2005:5009 USPATFULL  
 TITLE: Compounds for the treatment of metabolic disorders  
 INVENTOR(S): Sharma, Shalini, Gaithersburg, MD, UNITED STATES  
 von Borstel, Reid W., Potomac, MD, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2005004115	A1	20050106
APPLICATION INFO.:	US 2004-892950	A1	20040716 (10)
RELATED APPLN. INFO.:	Division of Ser. No. US 2003-685183, filed on 14 Oct 2003, PENDING Division of Ser. No. US 2002-167839, filed on 12 Jun 2002, PENDING		

	NUMBER	DATE
PRIORITY INFORMATION:	US 2001-297282P	20010612 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	LEWIS J. KREISLER, LEGAL DEPARTMENT, 930 CLOPPER ROAD, GAIITHERSBURG, MD, 20878	
NUMBER OF CLAIMS:	6	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	2 Drawing Page(s)	
LINE COUNT:	4295	
CAS INDEXING IS AVAILABLE FOR THIS PATENT.		
AB	Compounds useful for the treatment of various metabolic disorders, such as insulin resistance syndrome, diabetes, hyperlipidemia, fatty liver disease, cachexia, obesity, atherosclerosis and arteriosclerosis, are disclosed.	
IT	<b>478162-92-4P</b> (preparation of benzyloxyphenyloxobutyrates and related compds. for treatment of metabolic disorders)	
RN	478162-92-4 USPATFULL	
CN	Benzenebutanamide, 3-[(2,6-dimethylphenyl)methoxy]-N-hydroxy- $\gamma$ -oxo- (9CI) (CA INDEX NAME)	



L66 ANSWER 17 OF 26 USPATFULL on STN  
 ACCESSION NUMBER: 2004:335929 USPATFULL  
 TITLE: Compounds for the treatment of metabolic disorders  
 INVENTOR(S): Sharma, Shalini, Gaithersburg, MD, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004267025	A1	20041230
APPLICATION INFO.:	US 2003-684740	A1	20031014 (10)
RELATED APPLN. INFO.:	Division of Ser. No. US 2002-167839, filed on 12 Jun 2002, PENDING		

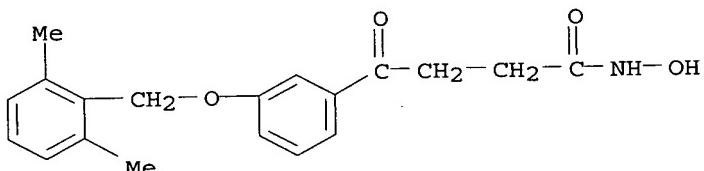
	NUMBER	DATE
PRIORITY INFORMATION:	US 2001-297282P	20010612 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	LEWIS J. KREISLER, LEGAL DEPARTMENT, 930 CLOPPER ROAD, GAIITHERSBURG, MD, 20878	
NUMBER OF CLAIMS:	6	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	2 Drawing Page(s)	
LINE COUNT:	4304	
CAS INDEXING IS AVAILABLE FOR THIS PATENT.		
AB	Compounds useful for the treatment of various metabolic disorders, such	

as insulin resistance syndrome, diabetes, hyperlipidemia, fatty liver disease, cachexia, obesity, atherosclerosis and arteriosclerosis, are disclosed.

IT 478162-92-4P  
 (preparation of benzyloxyphenyloxobutyrates and related compds. for treatment of metabolic disorders)

RN 478162-92-4 USPATFULL

CN Benzenebutanamide, 3-[(2,6-dimethylphenyl)methoxy]-N-hydroxy- $\gamma$ -oxo-(9CI) (CA INDEX NAME)



L66 ANSWER 18 OF 26 USPATFULL on STN

ACCESSION NUMBER: 2004:308016 USPATFULL  
 TITLE: Compounds for the treatment of metabolic disorders  
 INVENTOR(S): Sharma, Shalini, Gaithersburg, MD, UNITED STATES  
 von Borstel, Reid W., Potomac, MD, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004242692	A1	20041202
APPLICATION INFO.:	US 2004-865088	A1	20040610 (10)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 2002-167839, filed on 12 Jun 2002, PENDING		

	NUMBER	DATE
PRIORITY INFORMATION:	US 2001-297282P	20010612 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	LEWIS J. KREISLER, LEGAL DEPARTMENT, 930 CLOPPER ROAD, GAITHERSBURG, MD, 20878	

NUMBER OF CLAIMS: 44  
 EXEMPLARY CLAIM: 1

NUMBER OF DRAWINGS: 2 Drawing Page(s)

LINE COUNT: 4400

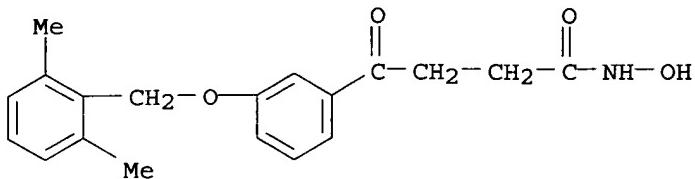
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Compounds useful for the treatment of various metabolic disorders, such as insulin resistance syndrome, diabetes, hyperlipidemia, fatty liver disease, cachexia, obesity, atherosclerosis and arteriosclerosis, are disclosed.

IT 478162-92-4P  
 (preparation of benzyloxyphenyloxobutyrates and related compds. for treatment of metabolic disorders)

RN 478162-92-4 USPATFULL

CN Benzenebutanamide, 3-[(2,6-dimethylphenyl)methoxy]-N-hydroxy- $\gamma$ -oxo-(9CI) (CA INDEX NAME)



L66 ANSWER 19 OF 26 USPATFULL on STN

ACCESSION NUMBER: 2004:121102 USPATFULL

TITLE: Compounds for the treatment of metabolic disorders

INVENTOR(S): Sharma, Shalini, Gaithersburg, MD, UNITED STATES

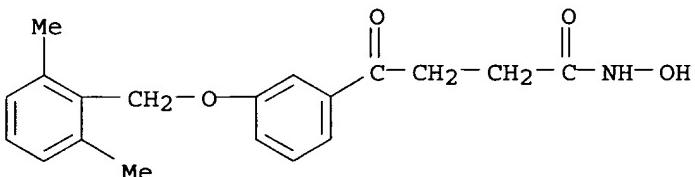
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004092518	A1	20040513
APPLICATION INFO.:	US 2003-684735	A1	20031014 (10)
RELATED APPLN. INFO.:	Division of Ser. No. US 2002-167839, filed on 12 Jun 2002, PENDING		

	NUMBER	DATE
PRIORITY INFORMATION:	US 2001-297282P	20010612 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	LEWIS J. KREISLER, LEGAL DEPARTMENT, 930 CLOPPER ROAD, GAITHERSBURG, MD, 20878	
NUMBER OF CLAIMS:	3	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	2 Drawing Page(s)	
LINE COUNT:	4261	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

**AB** Compounds useful for the treatment of various metabolic disorders, such as insulin resistance syndrome, diabetes, hyperlipidemia, fatty liver disease, cachexia, obesity, atherosclerosis and arteriosclerosis, are disclosed.

**IT 478162-92-4P**  
(preparation of benzyloxypyhenyloxobutyrates and related compds. for treatment of metabolic disorders)

**RN 478162-92-4 USPATFULL****CN Benzenebutanamide, 3-[(2,6-dimethylphenyl)methoxy]-N-hydroxy-gamma-oxo- (9CI) (CA INDEX NAME)**

L66 ANSWER 20 OF 26 USPATFULL on STN

ACCESSION NUMBER: 2004:83242 USPATFULL

TITLE: Hydantoin derivatives as inhibitors of matrix

INVENTOR(S) : metalloproteinases and/or TNF-alpha converting enzyme  
 Maduskuie, Thomas P., Wilmington, DE, UNITED STATES

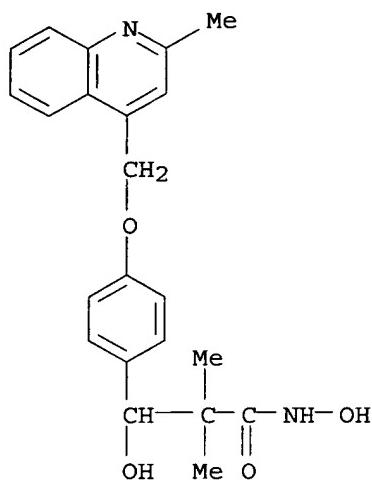
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004063698	A1	20040401
APPLICATION INFO.:	US 2003-632197	A1	20030731 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2002-400237P	20020801 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	STEPHEN B. DAVIS, BRISTOL-MYERS SQUIBB COMPANY, PATENT DEPARTMENT, P O BOX 4000, PRINCETON, NJ, 08543-4000	
NUMBER OF CLAIMS:	18	
EXEMPLARY CLAIM:	1	
LINE COUNT:	3217	
CAS INDEXING IS AVAILABLE FOR THIS PATENT.		
AB	The present invention provides compounds of Formula (I): ##STR1##	

or a stereoisomer or pharmaceutically acceptable salt form thereof, wherein the variables A, R.sup.1, R.sup.2, R.sup.3, R.sup.4, Z, U, X, Y, Z.sup.a, and n are defined are as defined herein, which are useful as inhibitors of matrix metalloproteinases (MMP) and/or TNF- $\alpha$  converting enzyme (TACE), or a combination thereof.

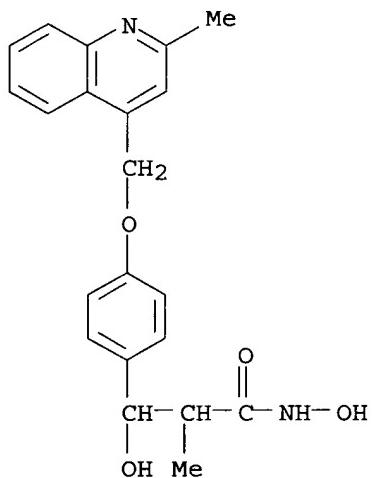
IT 656802-67-4P 656802-68-5P 656802-69-6P  
 656802-70-9P 656802-71-0P 656802-72-1P  
 656802-73-2P 656802-74-3P 656802-75-4P  
 656802-76-5P 656802-77-6P 656802-78-7P  
 656802-79-8P 656802-80-1P 656802-81-2P  
 656802-82-3P 656802-83-4P 656802-84-5P  
 656802-85-6P 656802-86-7P 656802-87-8P  
 656802-88-9P 656802-89-0P 656802-90-3P  
 656802-91-4P 656802-92-5P 656803-05-3P  
 656803-06-4P 656803-07-5P 656803-08-6P  
 656803-09-7P 656803-11-1P 656803-12-2P  
 656803-14-4P 656803-16-6P 656803-18-8P  
 656803-20-2P 656803-22-4P 656803-24-6P  
 656803-26-8P 656803-28-0P 656803-30-4P  
 656803-32-6P 656803-33-7P 656803-35-9P  
 656803-36-0P  
 (hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNF $\alpha$  converting enzyme for use in treatment of diseases)

RN 656802-67-4 USPATFULL  
 CN Benzenepropanamide, N, $\beta$ -dihydroxy- $\alpha$ , $\alpha$ -dimethyl-4-[(2-methyl-4-quinolinyl)methoxy]- (9CI) (CA INDEX NAME)



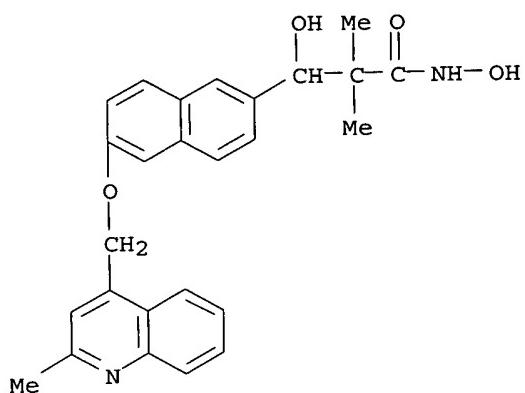
RN 656802-68-5 USPATFULL

CN Benzenepropanamide, N,β-dihydroxy-α-methyl-4-[(2-methyl-4-quinolinyl)methoxy]- (9CI) (CA INDEX NAME)

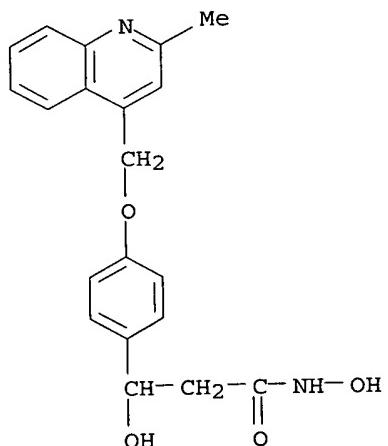


RN 656802-69-6 USPATFULL

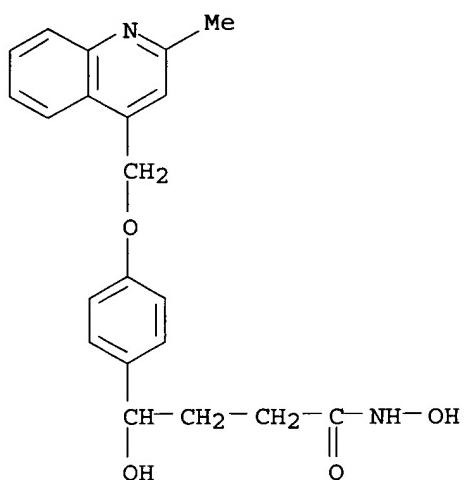
CN 2-Naphthalenepropanamide, N,β-dihydroxy-α,α-dimethyl-6-[(2-methyl-4-quinolinyl)methoxy]- (9CI) (CA INDEX NAME)



RN 656802-70-9 USPATFULL  
 CN Benzenepropanamide, N,β-dihydroxy-4-[(2-methyl-4-quinolinyl)methoxy] -  
 (9CI) (CA INDEX NAME)

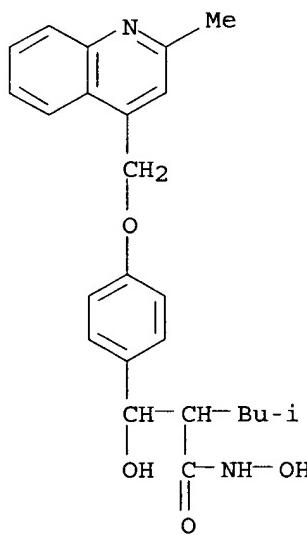


RN 656802-71-0 USPATFULL  
 CN Benzenebutanamide, N,γ-dihydroxy-4-[(2-methyl-4-quinolinyl)methoxy] -  
 (9CI) (CA INDEX NAME)



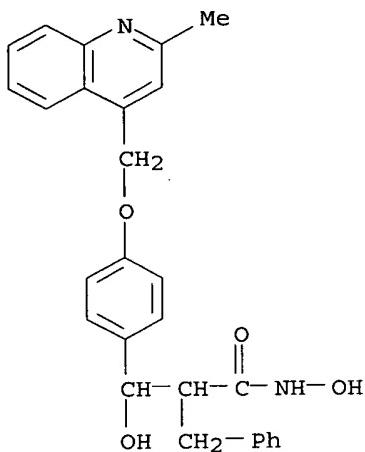
RN 656802-72-1 USPATFULL

CN Benzenepropanamide, N,β-dihydroxy-α-(2-methylpropyl)-4-[(2-methyl-4-quinolinyl)methoxy] - (9CI) (CA INDEX NAME)



RN 656802-73-2 USPATFULL

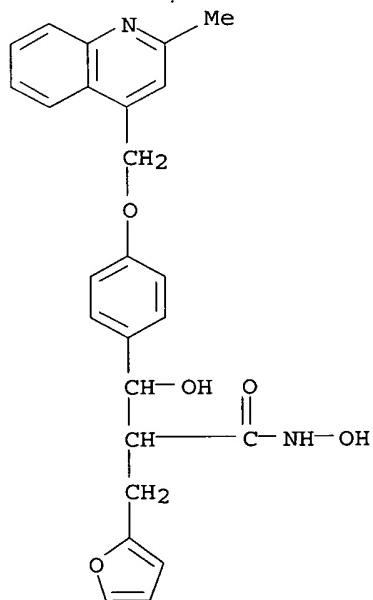
CN Benzenepropanamide, N,β-dihydroxy-4-[(2-methyl-4-quinolinyl)methoxy]-α-(phenylmethyl) - (9CI) (CA INDEX NAME)



RN 656802-74-3 USPATFULL

CN 2-Furanpropanamide, N-hydroxy-alpha-[hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]- (9CI) (CA INDEX NAME)

PAGE 1-A

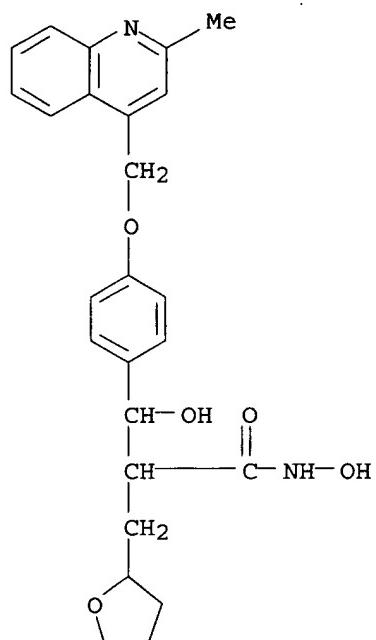


PAGE 2-A

RN 656802-75-4 USPATFULL

CN 2-Furanpropanamide, tetrahydro-N-hydroxy-alpha-[hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]- (9CI) (CA INDEX NAME)

PAGE 1-A

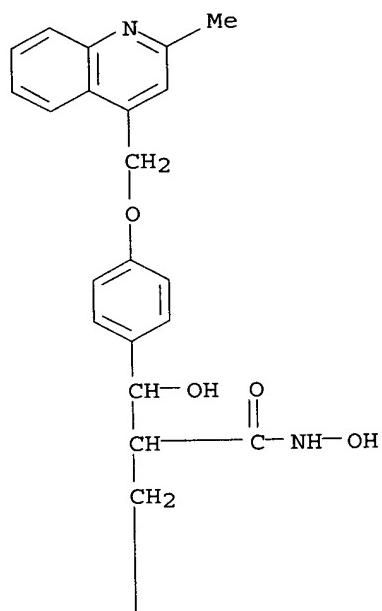


PAGE 2-A

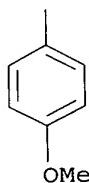
RN 656802-76-5 USPATFULL

CN Benzene propanamide, N,β-dihydroxy-α-[(4-methoxyphenyl)methyl]-4-[(2-methyl-4-quinolinyl)methoxy] - (9CI) (CA INDEX NAME)

PAGE 1-A

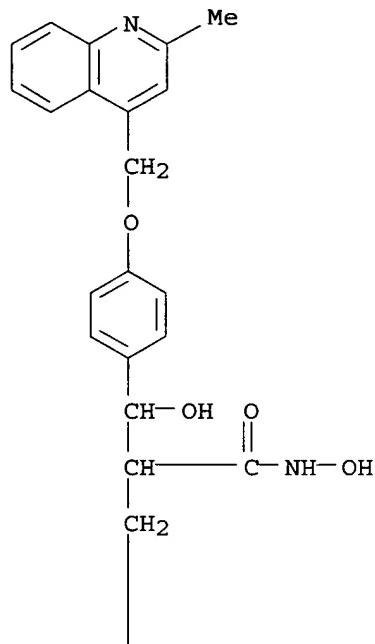


PAGE 2-A

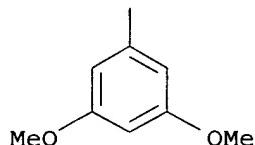


RN 656802-77-6 USPATFULL  
 CN Benzenepropanamide, N-hydroxy- $\alpha$ -[hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-3,5-dimethoxy- (9CI) (CA INDEX NAME)

PAGE 1-A

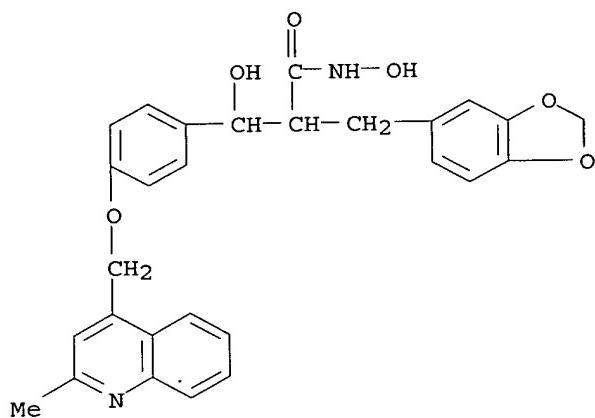


PAGE 2-A



RN 656802-78-7 USPATFULL

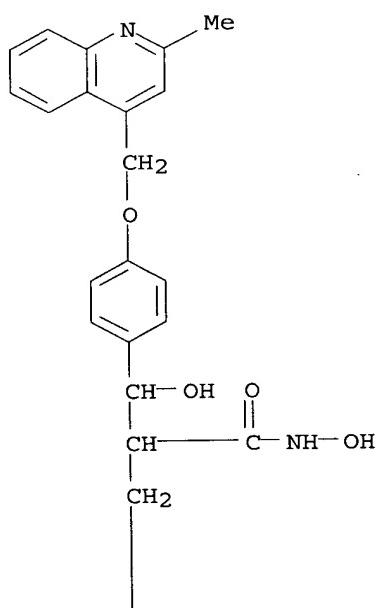
CN 1,3-Benzodioxole-5-propanamide, N-hydroxy- $\alpha$ -[hydroxy[4-[2-methyl-4-quinolinyl]methoxy]phenyl]methyl] - (9CI) (CA INDEX NAME)



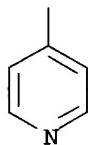
RN 656802-79-8 USPATFULL

CN 4-Pyridinepropanamide, N-hydroxy- $\alpha$ -[hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]- (9CI) (CA INDEX NAME)

PAGE 1-A



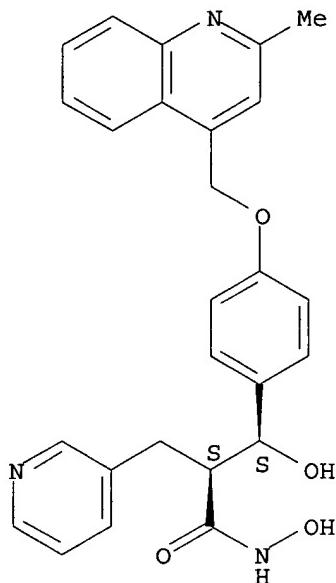
PAGE 2-A



RN 656802-80-1 USPATFULL

CN 3-Pyridinepropanamide, N-hydroxy- $\alpha$ -[(R)-hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-, ( $\alpha$ R)-rel- (9CI) (CA INDEX NAME)

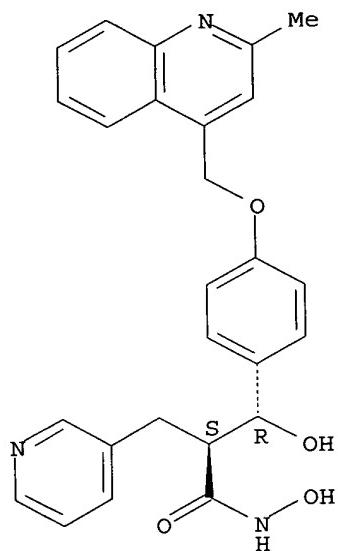
Relative stereochemistry.



RN 656802-81-2 USPATFULL

CN 3-Pyridinepropanamide, N-hydroxy- $\alpha$ -[(R)-hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-, ( $\alpha$ S)-rel- (9CI) (CA INDEX NAME)

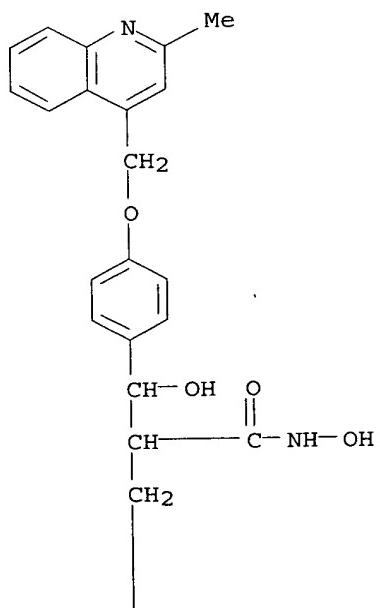
Relative stereochemistry.



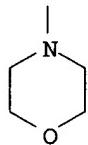
RN 656802-82-3 USPATFULL

CN 4-Morpholinepropanamide, N-hydroxy- $\alpha$ -[hydroxy[4-[(2-methyl-4-quinolinyl)methoxyphenyl]methyl]- (9CI) (CA INDEX NAME)

PAGE 1-A



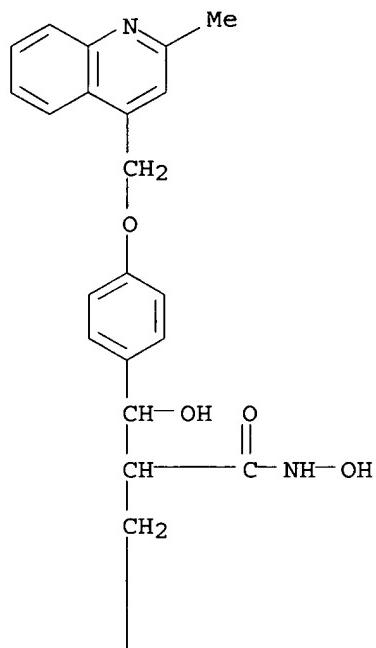
PAGE 2-A



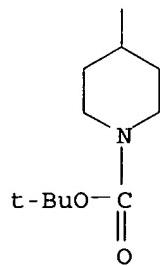
RN 656802-83-4 USPATFULL

CN 1-Piperidinocarboxylic acid, 4-[3-(hydroxyamino)-2-[hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-3-oxopropyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

PAGE 1-A



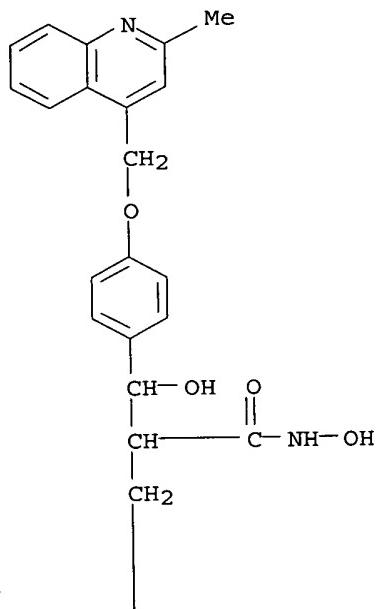
PAGE 2 -A



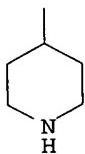
RN 656802-84-5 USPATFULL

CN 4-Piperidinepropanamide, N-hydroxy- $\alpha$ -[hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]- (9CI) (CA INDEX NAME)

PAGE 1-A

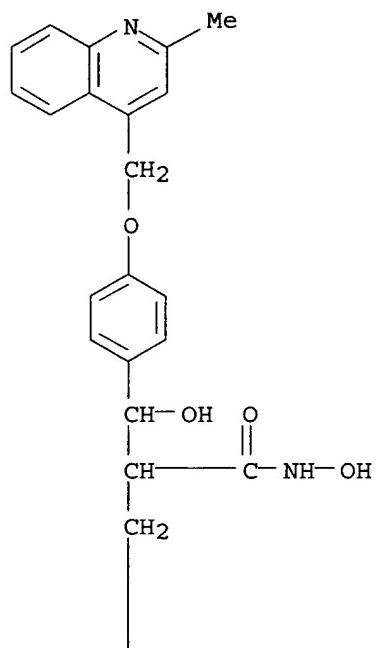


PAGE 2-A

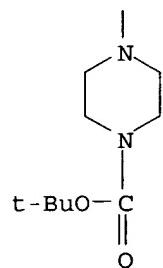


RN 656802-85-6 USPATFULL  
CN 1-Piperazinecarboxylic acid, 4-[3-(hydroxyamino)-2-[hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-3-oxopropyl]-, 1,1-dimethylethyl ester  
(9CI) (CA INDEX NAME)

PAGE 1-A



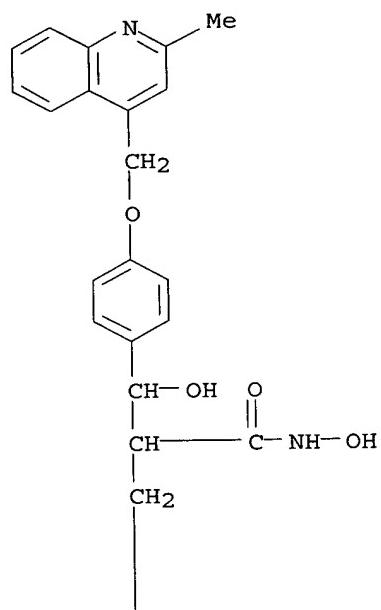
PAGE 2-A



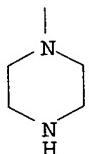
RN 656802-86-7 USPATFULL

CN 1-Piperazinepropanamide, N-hydroxy- $\alpha$ -[hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]- (9CI) (CA INDEX NAME)

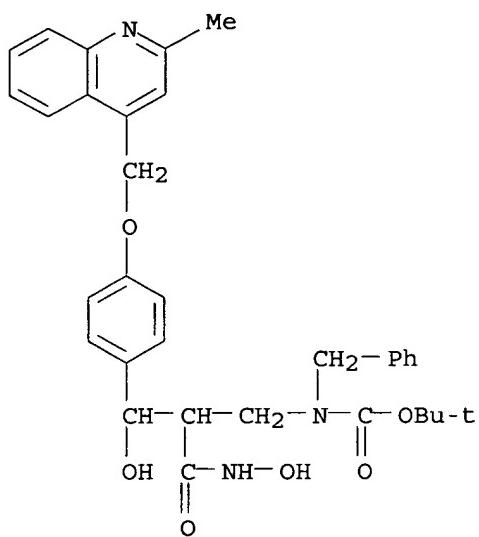
PAGE 1-A



PAGE 2-A

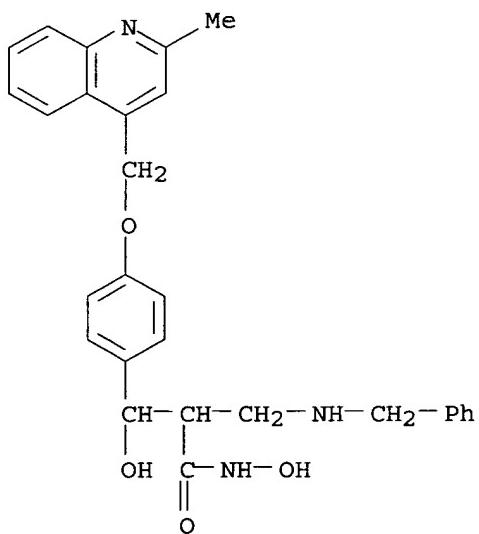


RN 656802-87-8 USPATFULL  
 CN Carbamic acid, [3-(hydroxyamino)-2-[hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-3-oxopropyl](phenylmethyl)-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



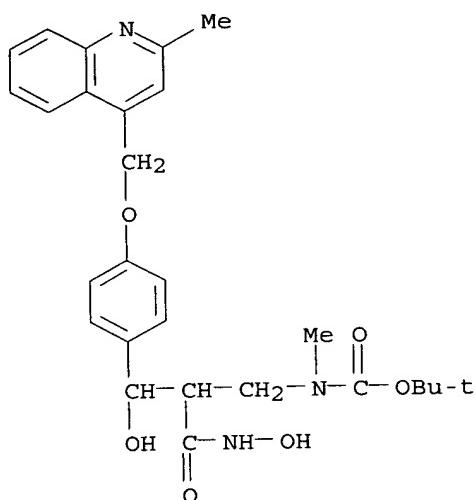
RN 656802-88-9 USPATFULL

CN Benzenepropanamide, N,β-dihydroxy-4-[(2-methyl-4-quinolinyl)methoxy]-  
 $\alpha$ -[(phenylmethyl)amino]methyl- (9CI) (CA INDEX NAME)

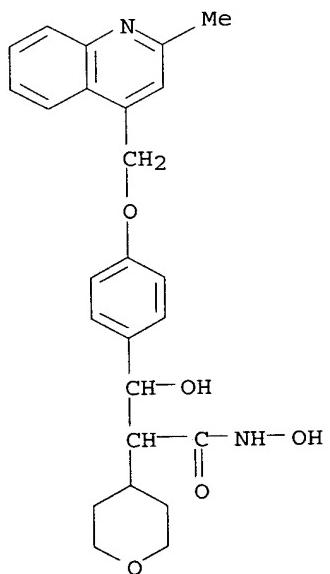


RN 656802-89-0 USPATFULL

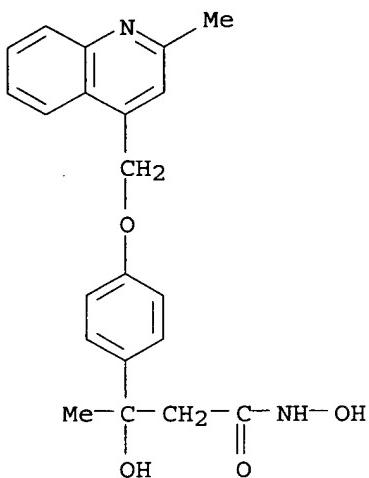
CN Carbamic acid, [3-(hydroxyamino)-2-[hydroxy[4-[(2-methyl-4-  
 quinolinyl)methoxy]phenyl]methyl]-3-oxopropyl]methyl-, 1,1-dimethylethyl  
 ester (9CI) (CA INDEX NAME)



RN 656802-90-3 USPATFULL  
 CN 2H-Pyran-4-acetamide, tetrahydro-N-hydroxy-alpha-[hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]- (9CI) (CA INDEX NAME)

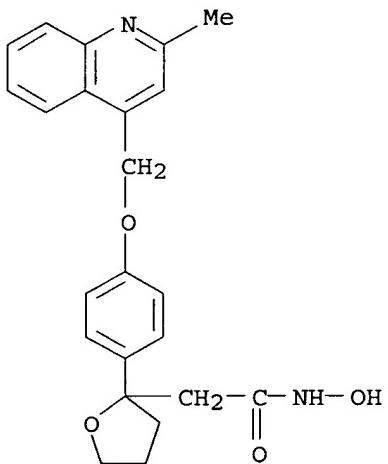


RN 656802-91-4 USPATFULL  
 CN Benzenepropanamide, N,β-dihydroxy-β-methyl-4-[(2-methyl-4-quinolinyl)methoxy]- (9CI) (CA INDEX NAME)



RN 656802-92-5 USPATFULL

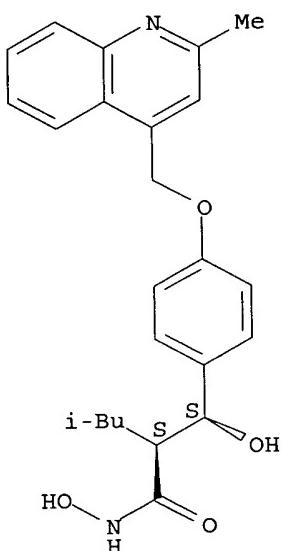
CN 2-Furanacetamide, tetrahydro-N-hydroxy-2-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]- (9CI) (CA INDEX NAME)



RN 656803-05-3 USPATFULL

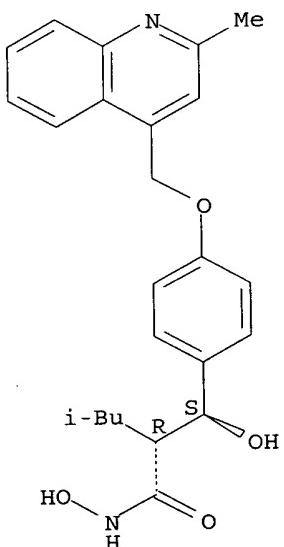
CN Benzenepropanamide, N,β-dihydroxy-α-(2-methylpropyl)-4-[(2-methyl-4-quinolinyl)methoxy]-, (αR,βR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



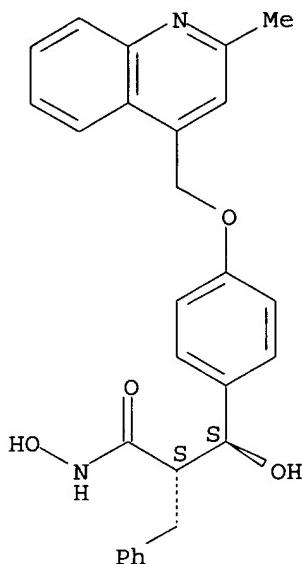
RN 656803-06-4 USPATFULL  
 CN Benzene propanamide, N,β-dihydroxy-α-(2-methylpropyl)-4-[(2-methyl-4-quinolinyl)methoxy]-, (αR,βS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RN 656803-07-5 USPATFULL  
 CN Benzene propanamide, N,β-dihydroxy-4-[(2-methyl-4-quinolinyl)methoxy]-α-(phenylmethyl)-, (αR,βR)-rel- (9CI) (CA INDEX NAME)

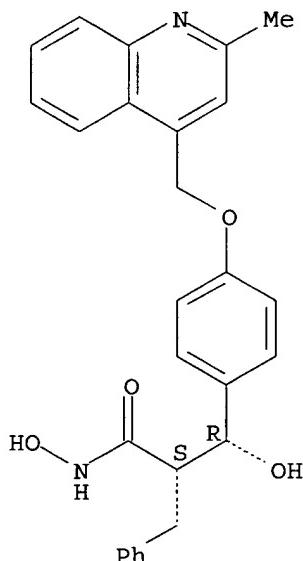
Relative stereochemistry.



RN 656803-08-6 USPATFULL

CN Benzenepropanamide, N,β-dihydroxy-4-[(2-methyl-4-quinolinyl)methoxy]-  
 $\alpha$ - (phenylmethyl)-, ( $\alpha$ R, $\beta$ S)-rel- (9CI) (CA INDEX NAME)

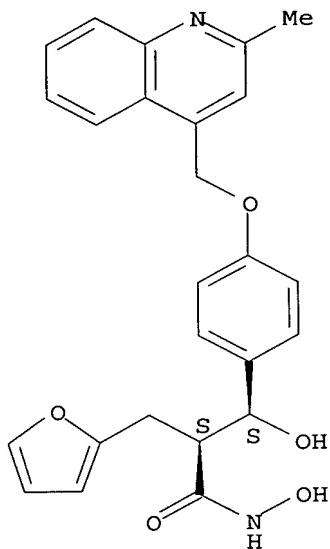
Relative stereochemistry.



RN 656803-09-7 USPATFULL

CN 2-Furanpropanamide, N-hydroxy- $\alpha$ -[(R)-hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-, ( $\alpha$ R)-rel- (9CI) (CA INDEX NAME)

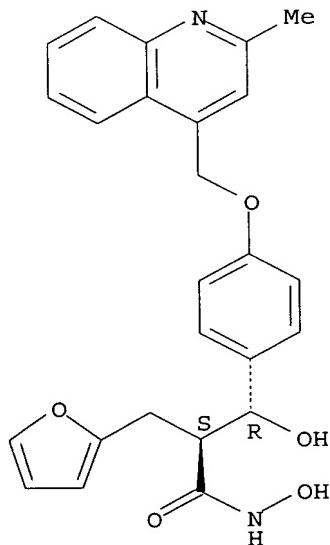
Relative stereochemistry.



RN 656803-11-1 USPATFULL

CN 2-Furanpropanamide, N-hydroxy- $\alpha$ -[(R)-hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-, ( $\alpha$ S)-rel- (9CI) (CA INDEX NAME)

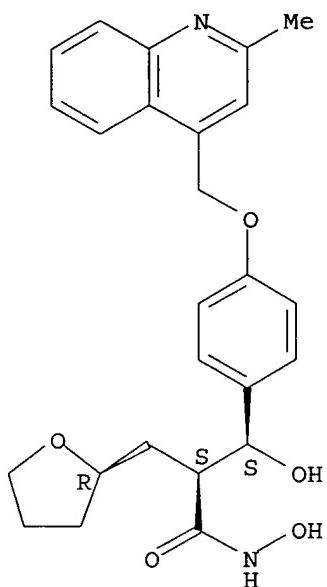
Relative stereochemistry.



RN 656803-12-2 USPATFULL

CN 2-Furanpropanamide, tetrahydro-N-hydroxy- $\alpha$ -[(R)-hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-, ( $\alpha$ R,2S)-rel- (9CI) (CA INDEX NAME)

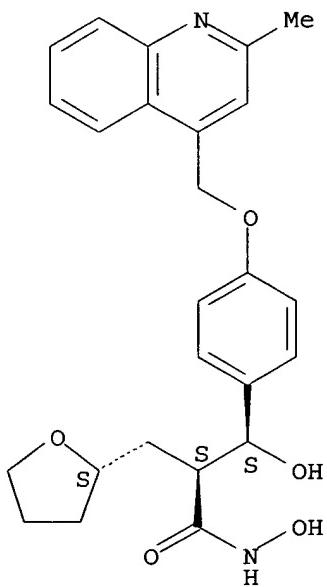
Relative stereochemistry.



RN 656803-14-4 USPATFULL

CN 2-Furanpropanamide, tetrahydro-N-hydroxy-alpha-[(R)-hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-, (alpha R, 2R)-rel- (9CI) (CA INDEX NAME)

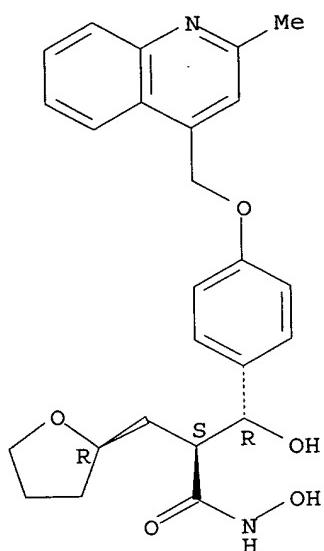
Relative stereochemistry.



RN 656803-16-6 USPATFULL

CN 2-Furanpropanamide, tetrahydro-N-hydroxy-alpha-[(S)-hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-, (alpha S, 2R)-rel- (9CI) (CA INDEX NAME)

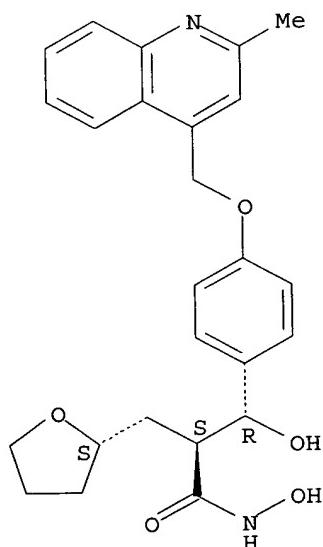
Relative stereochemistry.



RN 656803-18-8 USPATFULL

CN 2-Furanpropanamide, tetrahydro-N-hydroxy- $\alpha$ -[(R)-hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-, ( $\alpha$ S,2S)-rel- (9CI) (CA INDEX NAME)

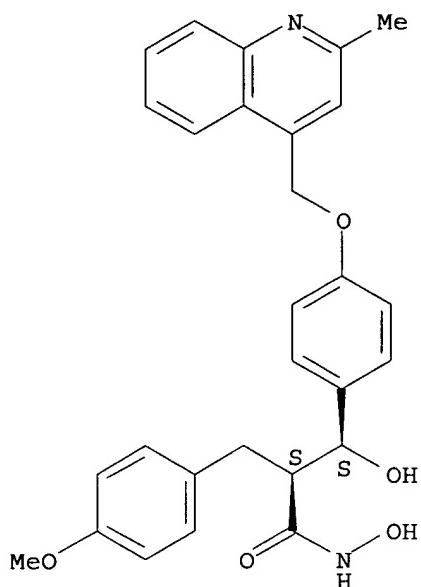
Relative stereochemistry.



RN 656803-20-2 USPATFULL

CN Benzene propanamide, N, $\beta$ -dihydroxy- $\alpha$ -[(4-methoxyphenyl)methyl]-4-[(2-methyl-4-quinolinyl)methoxy]-, ( $\alpha$ R, $\beta$ R)-rel- (9CI) (CA INDEX NAME)

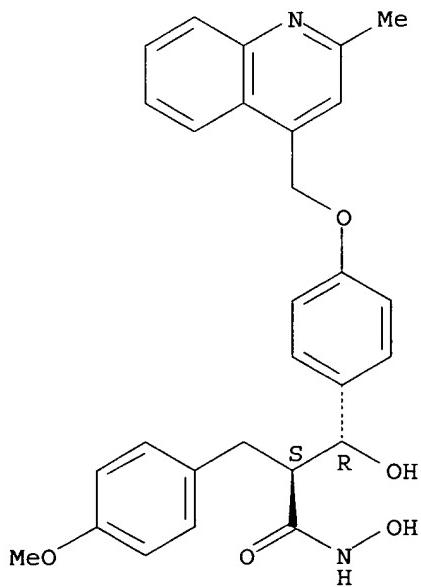
Relative stereochemistry.



RN 656803-22-4 USPATFULL

CN Benzenepropanamide, N,β-dihydroxy-α-[(4-methoxyphenyl)methyl]-4-[ (2-methyl-4-quinolinyl)methoxy]-, (αR,βS)-rel- (9CI) (CA INDEX NAME)

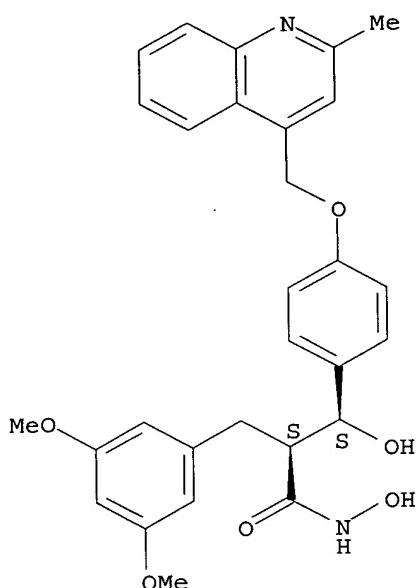
Relative stereochemistry.



RN 656803-24-6 USPATFULL

CN Benzenepropanamide, N-hydroxy-α-[(R)-hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-3,5-dimethoxy-, (αR)-rel- (9CI) (CA INDEX NAME)

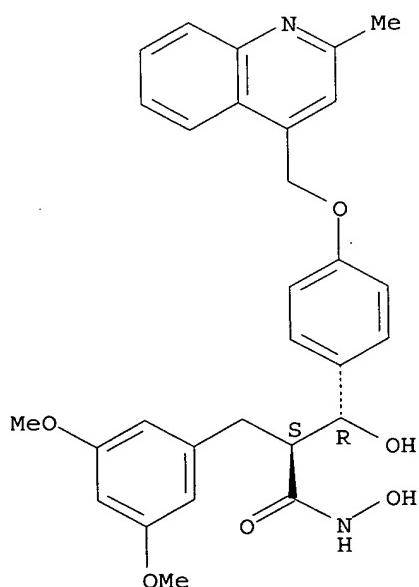
Relative stereochemistry.



RN 656803-26-8 USPATFULL

CN Benzenepropanamide, N-hydroxy- $\alpha$ -[ (R)-hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-3,5-dimethoxy-, ( $\alpha$ S)-rel- (9CI)  
(CA INDEX NAME)

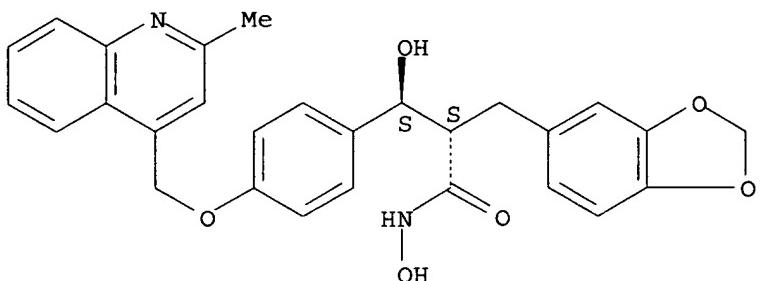
Relative stereochemistry.



RN 656803-28-0 USPATFULL

CN 1,3-Benzodioxole-5-propanamide, N-hydroxy- $\alpha$ -[ (R)-hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-, ( $\alpha$ R)-rel- (9CI) (CA INDEX NAME)

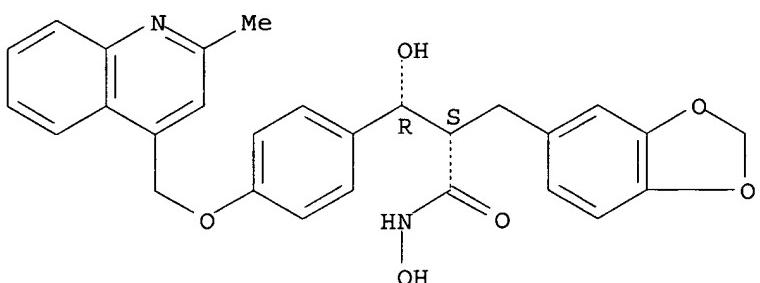
Relative stereochemistry.



RN 656803-30-4 USPATFULL

CN 1,3-Benzodioxole-5-propanamide, N-hydroxy- $\alpha$ -[(R)-hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-, ( $\alpha$ S)-rel- (9CI) (CA INDEX NAME)

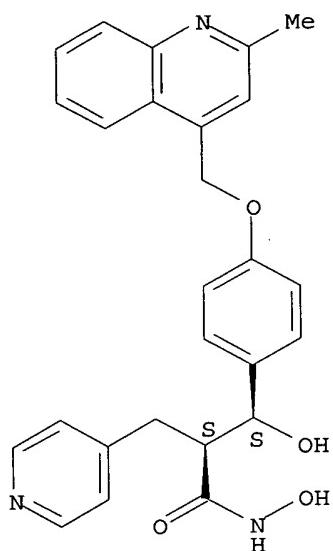
Relative stereochemistry.



RN 656803-32-6 USPATFULL

CN 4-Pyridinepropanamide, N-hydroxy- $\alpha$ -[(R)-hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-, ( $\alpha$ R)-rel- (9CI) (CA INDEX NAME)

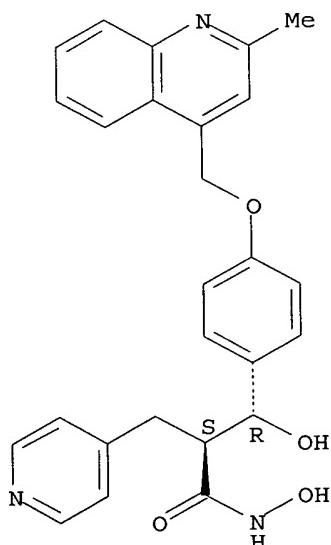
Relative stereochemistry.



RN 656803-33-7 USPATFULL

CN 4-Pyridinepropanamide, N-hydroxy- $\alpha$ -[(R)-hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-, ( $\alpha$ S)-rel- (9CI) (CA INDEX NAME)

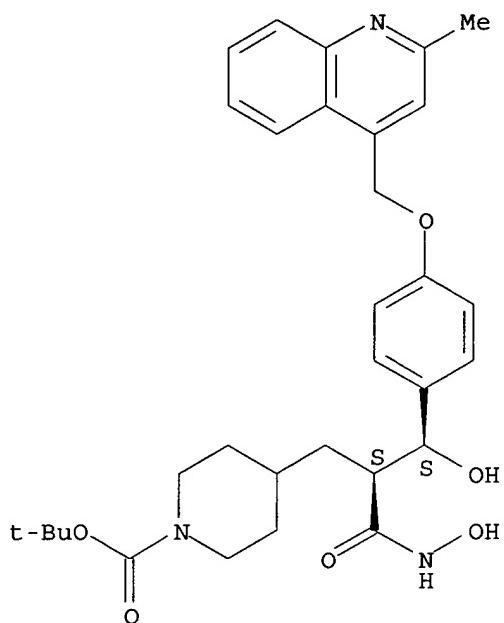
Relative stereochemistry.



RN 656803-35-9 USPATFULL

CN 1-Piperidincarboxylic acid, 4-[(2R)-3-(hydroxyamino)-2-[(R)-hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-3-oxopropyl]-, 1,1-dimethylethyl ester, rel- (9CI) (CA INDEX NAME)

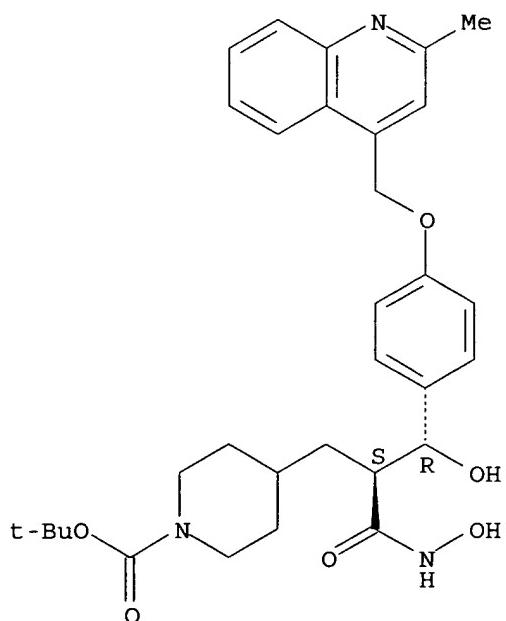
Relative stereochemistry.



RN 656803-36-0 USPATFULL

CN 1-Piperidinecarboxylic acid, 4-[(2R)-3-(hydroxyamino)-2-[(S)-hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-3-oxopropyl]-, 1,1-dimethylethyl ester, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



L66 ANSWER 21 OF 26 USPATFULL on STN

ACCESSION NUMBER: 2003:214464 USPATFULL

TITLE: Compounds for the treatment of metabolic disorders

## INVENTOR(S) :

Sharma, Shalini, Gaithersburg, MD, UNITED STATES  
 von Borstel, Reid W., Potomac, MD, UNITED STATES

PATENT INFORMATION:  
 APPLICATION INFO.:

NUMBER	KIND	DATE
US 2003149107	A1	20030807
US 2002-167839	A1	20020612 (10)

## PRIORITY INFORMATION:

NUMBER	DATE
US 2001-297282P	20010612 (60)

DOCUMENT TYPE:

Utility

FILE SEGMENT:

APPLICATION

LEGAL REPRESENTATIVE:

LEWIS J. KREISLER, LEGAL DEPARTMENT, 930 CLOPPER ROAD,  
 GAITHERSBURG, MD, 20878

NUMBER OF CLAIMS:

161

EXEMPLARY CLAIM:

1

NUMBER OF DRAWINGS:

2 Drawing Page(s)

LINE COUNT:

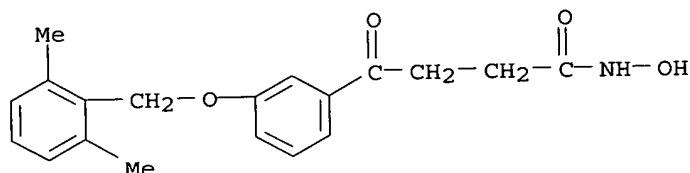
5232

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Compounds useful for the treatment of various metabolic disorders, such as insulin resistance syndrome, diabetes, hyperlipidemia, fatty liver disease, cachexia, obesity, atherosclerosis and arteriosclerosis, are disclosed.

IT 478162-92-4P  
 (preparation of benzyloxyphenyloxobutyrates and related compds. for treatment of metabolic disorders)

RN 478162-92-4 USPATFULL

CN Benzenebutanamide, 3-[(2,6-dimethylphenyl)methoxy]-N-hydroxy- $\gamma$ -oxo-  
 (9CI) (CA INDEX NAME)

L66 ANSWER 22 OF 26 USPATFULL on STN

ACCESSION NUMBER: 96:27207 USPATFULL

TITLE: N-hydroxyureas as 5-lipoxygenase inhibitors and inhibitors of oxidative modification of low density lipoprotein

INVENTOR(S): Malamas, Michael S., Jamison, PA, United States  
 Nelson, James A., Washingtons Crossing, PA, United States

PATENT ASSIGNEE(S): American Home Products Corporation, Madison, NJ, United States (U.S. corporation)

NUMBER	KIND	DATE
--------	------	------

PATENT INFORMATION:	US 5504097	19960402
APPLICATION INFO.:	US 1995-423061	19950417 (8)
RELATED APPLN. INFO.:	Division of Ser. No. US 1993-148603, filed on 8 Nov 1993, now patented, Pat. No. US 5459154	
DOCUMENT TYPE:	Utility	

FILE SEGMENT: Granted  
 PRIMARY EXAMINER: Gerstl, Robert  
 LEGAL REPRESENTATIVE: Boswell, Jr., R. F.  
 NUMBER OF CLAIMS: 1  
 EXEMPLARY CLAIM: 1  
 LINE COUNT: 1039

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention relates to compounds having 5-lipoxygenase inhibiting properties and inhibition of oxidative modification of low density lipoprotein which have the formula: ##STR1## wherein: R.sup.1 and R.sup.3 are independently hydrogen, halogen, C.sub.1 -C.sub.6 alkyl, C.sub.1 -C.sub.6 alkoxy, trifluoromethyl, or C.sub.1 -C.sub.6 trifluoroalkoxy;

R.sup.2 is hydrogen or methyl;

R.sup.4 is hydrogen, methyl or hydroxy;

R.sup.5 is hydrogen, --NH.sub.2, C.sub.1 -C.sub.6 alkyl, aryl, aralkyl, or --N.dbd.C(CH.sub.3).sub.2 ;

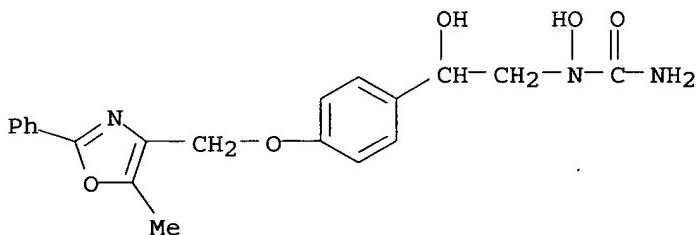
X and Y are independently O or S; and n is 0 or 1; or a pharmaceutically acceptable salt thereof. Compounds which inhibit 5-lipoxygenase are useful in the treatment of diseases mediated by leukotrienes such as inflammation or bronchoconstriction. Compounds which inhibit oxidative metabolism of low density lipoprotein are useful in the inhibition of atherosclerotic plaque formation.

IT 173191-84-9P

(N-hydroxy-N-[4-(2-phenyloxazolyl- and -thiazolylmethoxy)benzyl]ureas as 5-lipoxygenase inhibitors and inhibitors of oxidative modification of low d. lipoprotein)

RN 173191-84-9 USPATFULL

CN Urea, N-hydroxy-N-[2-hydroxy-2-[4-[(5-methyl-2-phenyl-4-oxazolyl)methoxy]phenyl]ethyl]- (9CI) (CA INDEX NAME)

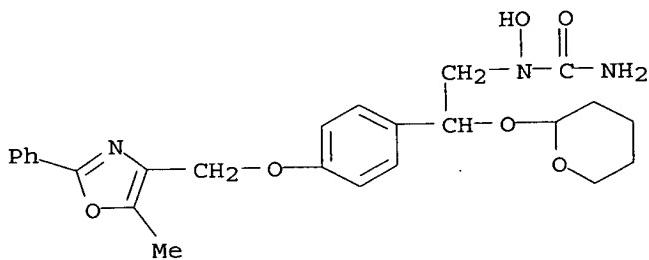


IT 173192-13-7P

(N-hydroxy-N-[4-(2-phenyloxazolyl- and -thiazolylmethoxy)benzyl]ureas as 5-lipoxygenase inhibitors and inhibitors of oxidative modification of low d. lipoprotein)

RN 173192-13-7 USPATFULL

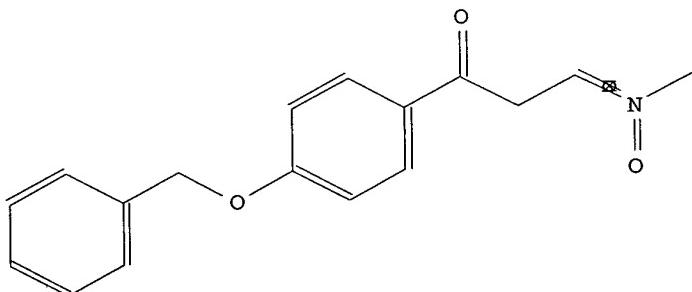
CN Urea, N-hydroxy-N-[2-[4-[(5-methyl-2-phenyl-4-oxazolyl)methoxy]phenyl]-2-[(tetrahydro-2H-pyran-2-yl)oxy]ethyl]- (9CI) (CA INDEX NAME)



=> d 166 ide 23  
YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS, USPATFULL, BEILSTEIN, CHEMCATS'  
CONTINUE? (Y)/N:Y

L66 ANSWER 23 OF 26 BEILSTEIN COPYRIGHT 2005 BEILSTEIN MDL on STN

Beilstein Records (BRN) :	5819891
Beilstein Pref. RN (BPR) :	143620-87-5
CAS Reg. No. (RN) :	<b>143620-87-5</b>
Molec. Formula (MF) :	C <sub>17</sub> H <sub>17</sub> N <sub>0</sub> O <sub>3</sub>
Molecular Weight (MW) :	283.33
Lawson Number (LN) :	9256, 5228, 3625
File Segment (FS) :	Stereo compound
Compound Type (CTYPE) :	isocyclic
Constitution ID (CONSID) :	5093914
Tautomer ID (TAUTID) :	5574652
Beilstein Citation (BSO) :	6-08
Entry Date (DED) :	1993/05/04
Update Date (DUPD) :	1994/02/18



#### Field Availability:

Code	Name	Occurrence
<hr/>		
BRN	Beilstein Records	1
BPR	Beilstein Preferred RN	1

RN	CAS Registry Number	1
MF	Molecular Formula	1
FW	Formular Weight	1
LN	Lawson Number	3
FS	File Segment	1
CTYPE	Compound Type	1
CONSID	Constitution ID	1
TAUTID	Tautomer ID	1
BSO	Beilstein Citation	1
DED	Entry Date	1
DUPD	Update Date	1
NMR	Nuclear Magnetic Resonance	3

This substance also occurs in Reaction Documents:

Code	Name	Occurrence
RX	Reaction Documents	1
RXPRO	Substance is Reaction Product	1

```
=> d rx 166 23
YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS, USPATFULL, BEILSTEIN, CHEMCATS' -
CONTINUE? (Y)/N:y
```

L66 ANSWER 23 OF 26 BEILSTEIN COPYRIGHT 2005 BEILSTEIN MDL on STN

Reaction:

RX

Reaction ID (.ID) :	1897053
Reactant BRN (.RBRN) :	1730792, 5815146
Reactant (.RCT) :	N-methyl-hydroxylamine, 1-(4-benzyloxy-phenyl)-3-dimethylamino- propanone
Product BRN (.PBRN) :	5852497, 5824062, 5819891, 5852496
Product (.PRO) :	1-(4-benzyloxy-phenyl)-3-(hydroxy-methyl- amino)-propanone, 5-(4-benzyloxy-phenyl)-2- methyl-2,5-dihydro-isoxazol-5-ol, C17H17NO3, 1-(4-benzyloxy-phenyl)-3- (hydroxy-methyl-amino)-propanone
No. of React. Details (.NVAR) :	1

Reaction Details:

RX

Reaction RID (.RID) :	1897053.1
Reaction Classification (.CL) :	Preparation
Reagent (.RGT) :	p-TsOH
Solvent (.SOL) :	methanol
Time (.TIM) :	30 min
Temperature (.T) :	20 Cel
Note(s) (.COM) :	Yield given. Yields of byproduct given. Title compound not separated from byproducts

Reference(s) :

- Wright, Stephen W.; Harris, Richard R.; Kerr, Janet S.; Green, Alicia M.; Pinto, Donald J.; et al., J.Med.Chem., CODEN: JMCMAR, 35(22), <1992>, 4061-4068; BABS-5706192

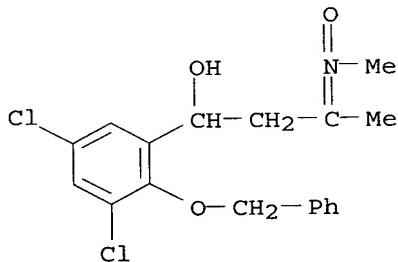
=> => d iall 166 24-26  
 YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS, USPATFULL, BEILSTEIN, CHEMCATS' -  
 CONTINUE? (Y)/N:y

'IALL' IS NOT A VALID FORMAT

In a multifile environment, a format can only be used if it is valid  
 in at least one of the files. Refer to file specific help messages  
 or the STNGUIDE file for information on formats available in  
 individual files.

REENTER DISPLAY FORMAT FOR ALL FILES (FILEDEFAULT):all

L66 ANSWER 24 OF 26 CHEMCATS COPYRIGHT 2005 ACS on STN  
 Accession No. (AN) : 2005:1864858 CHEMCATS  
 Catalog Name (CO) : Interchim Intermediates  
 Publication Date (PD) : 18 Jan 2005  
 Order Number (ON) : 7N-908  
 Chemical Name (CN) : Benzenemethanol, 3,5-dichloro- $\alpha$ -[2-(methyloxidoimino)propyl]-2-(phenylmethoxy)-  
 CAS Registry No. (RN) : 339020-55-2  
 Supplementary Term (ST) : CHEMICAL LIBRARY  
 Structure :



#### PRICES

Quantity : milligram quantities, Price: contact supplier

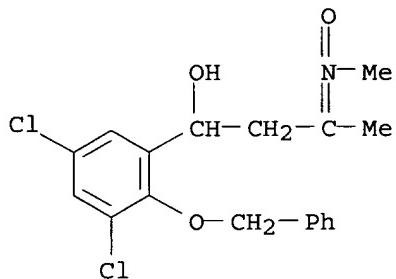
#### COMPANY INFORMATION

Interchim  
 211 bis Av J.F. Kennedy  
 BP 1140  
 Montlucon, 03103  
 France

Phone: (33) (0) 4 70 03 88 55  
 Fax: (33) (0) 4 70 03 82 60  
 Email: interchim@interchim.com  
 Web: http://www.interchim.com

L66 ANSWER 25 OF 26 CHEMCATS COPYRIGHT 2005 ACS on STN  
 Accession No. (AN) : 2004:278246 CHEMCATS  
 Catalog Name (CO) : Ambinter Stock Screening Collection  
 Publication Date (PD) : 1 Jan 2004

Order Number (ON) : 7N-908  
 Chemical Name (CN) : Benzenemethanol, 3,5-dichloro- $\alpha$ -[2-(methyloxidoimino)propyl]-2-(phenylmethoxy)-  
 CAS Registry No. (RN) : 339020-55-2  
 Supplementary Term (ST) : CHEMICAL LIBRARY  
 Structure :



## PRICES

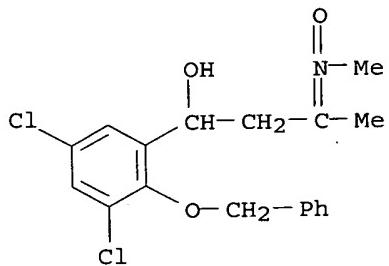
Quantity : milligram quantities, Price: contact supplier

## COMPANY INFORMATION

**Ambinter**  
 46 quai Louis Bleriot  
 Paris, F-75016  
 France

Phone: (33-1) 45 24 48 60  
 Fax: (33-1) 45 24 62 41  
 Email: ambinter@compuserve.com  
 Web: <http://www.ambinter.com>

L66 ANSWER 26 OF 26 CHEMCATS COPYRIGHT 2005 ACS on STN  
 Accession No. (AN) : 1999:148115 CHEMCATS  
 Catalog Name (CO) : Bionet Screening Compounds  
 Publication Date (PD) : 25 May 2005  
 Order Number (ON) : 7N-908  
 Chemical Name (CN) : { (E) -3-[2-(benzyloxy)-3,5-dichlorophenyl]-3-hydroxy-1-methylpropylidene} (methyl) ammoniumolate  
 CAS Registry No. (RN) : 339020-55-2  
 Supplementary Term (ST) : CHEMICAL LIBRARY  
 Structure :



## PRICES

Quantity : milligram quantities, Price: contact supplier

## COMPANY INFORMATION

Bionet Research Ltd.  
 Highfield Industrial Estate  
 Camelford, Cornwall, PL32 9QZ  
 United Kingdom

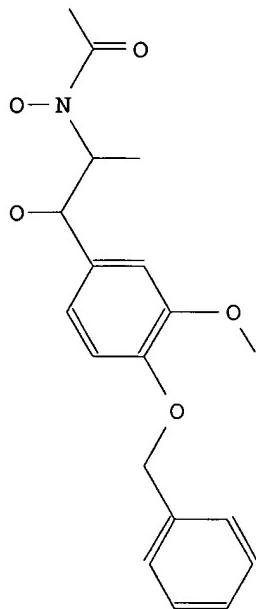
Phone: +44(0) 1840 212171  
 Fax: +44(0) 1840 213712  
 Email: [enquiries@keyorganics.ltd.uk](mailto:enquiries@keyorganics.ltd.uk)  
 Web: <http://www.bionetresearch.co.uk>

=> d que nos 163  
 L57 STR  
 L62 2 SEA FILE=BEILSTEIN SSS FUL L57  
 L63 1 SEA FILE=BEILSTEIN ABB=ON PLU=ON L62 NOT RN/FA

=> d ide 163  
 YOU HAVE REQUESTED DATA FROM FILE 'BEILSTEIN' - CONTINUE? (Y)/N:y

L63 ANSWER 1 OF 1 BEILSTEIN COPYRIGHT 2005 BEILSTEIN MDL on STN

Beilstein Records (BRN) :	3483237
Chemical Name (CN) :	N-hydroxy-N-<2-hydroxy-2-(4-benzyloxy-3-methoxy-phenyl)-1-methyl-ethyl>-acetamide
Autonom Name (AUN) :	N-<2-(4-benzyloxy-3-methoxy-phenyl)-2-hydroxy-1-methyl-ethyl>-N-hydroxy-acetamide
Molec. Formula (MF) :	C19 H23 N O5
Molecular Weight (MW) :	345.39
Lawson Number (LN) :	16410, 5228, 1155, 289
Compound Type (CTYPE) :	isocyclic
Constitution ID (CONSID) :	3072587
Tautomer ID (TAUTID) :	3285330
Beilstein Citation (BSO) :	3-15-00-00039
Entry Date (DED) :	1990/02/15
Update Date (DUPD) :	1991/09/20



## Field Availability:

Code	Name	Occurrence
<hr/>		
BRN	Beilstein Records	1
CN	Chemical Name	1
AUN	Autonomname	1
MF	Molecular Formula	1
FW	Formular Weight	1
LN	Lawson Number	4
CTYPE	Compound Type	1
CONSID	Constitution ID	1
TAUTID	Tautomer ID	1
BSO	Beilstein Citation	1
DED	Entry Date	1
DUPD	Update Date	1
MP	Melting Point	1

This substance also occurs in Reaction Documents:

Code	Name	Occurrence
<hr/>		
RX	Reaction Documents	1
RXPRO	Substance is Reaction Product	1

```
=> d 163 rx
YOU HAVE REQUESTED DATA FROM FILE 'BEILSTEIN' - CONTINUE? (Y)/N:y
```

L63 ANSWER 1 OF 1 BEILSTEIN COPYRIGHT 2005 BEILSTEIN MDL on STN

## Reaction:

RX

Reaction ID (.ID) : 519302  
 Reactant BRN (.RBRN) : 3467878  
 Reactant (.RCT) : 1-acetoxy-1-(4-benzyloxy-3-methoxy-phenyl)-  
 2-nitro-propane  
 Product BRN (.PBRN) : 3222448, 3483237  
 Product (.PRO) : (1RS:2RS)-2-acetylamino-1-(3-methoxy-4-  
 benzyloxy-phenyl)-propanol-(1),  
 N-hydroxy-N-<2-hydroxy-2-(4-benzyloxy-3-  
 methoxy-phenyl)-1-methyl-ethyl>-acetamide  
 No. of React. Details (.NVAR) : 1

## Reaction Details:

RX

Reaction RID (.RID) : 519302.1  
 Reaction Classification (.CL) : Preparation  
 Reagent (.RGT) : ethanol, acetic acid, aqueous hydrochloric  
 acid  
 Temperature (.T) : 50 - 60 Cel  
 Other Conditions (.COND) : weiteres Reagens: Blei-Kathoden;  
 Behandlung der Reaktionsloesung mit  
 Natriumacetat  
 Note(s) (.COM) : Handbook  
 Reference(s) :  
 /l. v. Fodor, Chem.Ber., CODEN: CHBEAM, 76, <1943>, 1216, 1217, 1219

=&gt; file stnguide

FILE 'STNGUIDE' ENTERED AT 16:33:02 ON 11 OCT 2005  
 USE IS SUBJECT TO THE TERMS OF YOUR CUSTOMER AGREEMENT  
 COPYRIGHT (C) 2005 AMERICAN CHEMICAL SOCIETY, JAPAN SCIENCE  
 AND TECHNOLOGY CORPORATION, AND FACHINFORMATIONSZENTRUM KARLSRUHE

FILE CONTAINS CURRENT INFORMATION.

LAST RELOADED: Oct 7, 2005 (20051007/UP).

=&gt; =&gt; fil\_hcap

FILE 'HCAPLUS' ENTERED AT 14:43:44 ON 12 OCT 2005  
 USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.  
 PLEASE SEE "HELP USAGETERMS" FOR DETAILS.  
 COPYRIGHT (C) 2005 AMERICAN CHEMICAL SOCIETY (ACS)

Copyright of the articles to which records in this database refer is held by the publishers listed in the PUBLISHER (PB) field (available for records published or updated in Chemical Abstracts after December 26, 1996), unless otherwise indicated in the original publications. The CA Lexicon is the copyrighted intellectual property of the American Chemical Society and is provided to assist you in searching databases on STN. Any dissemination, distribution, copying, or storing of this information, without the prior written consent of CAS, is strictly prohibited.

FILE COVERS 1907 - 12 Oct 2005 VOL 143 ISS 16  
 FILE LAST UPDATED: 11 Oct 2005 (20051011/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> fil zcap

FILE 'ZCAPLUS' ENTERED AT 14:43:47 ON 12 OCT 2005  
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.  
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.  
COPYRIGHT (C) 2005 AMERICAN CHEMICAL SOCIETY (ACS)

Copyright of the articles to which records in this database refer is held by the publishers listed in the PUBLISHER (PB) field (available for records published or updated in Chemical Abstracts after December 26, 1996), unless otherwise indicated in the original publications. The CA Lexicon is the copyrighted intellectual property of the American Chemical Society and is provided to assist you in searching databases on STN. Any dissemination, distribution, copying, or storing of this information, without the prior written consent of CAS is strictly prohibited.

FILE COVERS 1907 - 12 Oct 2005 VOL 143 ISS 16  
FILE LAST UPDATED: 11 Oct 2005 (20051011/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> fil lreg

FILE 'LREGISTRY' ENTERED AT 14:43:50 ON 12 OCT 2005  
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.  
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.  
COPYRIGHT (C) 1985 AMERICAN CHEMICAL SOCIETY (ACS)

LREGISTRY IS A STATIC LEARNING FILE

NEW CAS INFORMATION USE POLICIES, ENTER HELP USAGETERMS FOR DETAILS.

=> fil reg

FILE 'REGISTRY' ENTERED AT 14:43:52 ON 12 OCT 2005  
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.  
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.  
COPYRIGHT (C) 2005 American Chemical Society (ACS)

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 11 OCT 2005 HIGHEST RN 865062-68-6  
DICTIONARY FILE UPDATES: 11 OCT 2005 HIGHEST RN 865062-68-6

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH JULY 14, 2005

Please note that search-term pricing does apply when conducting SmartSELECT searches.

```
*****
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added,   *
* effective March 20, 2005. A new display format, IDERL, is now      *
* available and contains the CA role and document type information. *
*****
```

Structure search iteration limits have been increased. See HELP SLIMITS for details.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

<http://www.cas.org/ONLINE/UG/regprops.html>

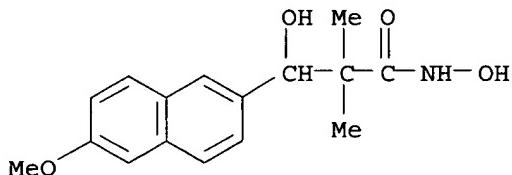
```
=> file stnguide
FILE 'STNGUIDE' ENTERED AT 14:43:54 ON 12 OCT 2005
USE IS SUBJECT TO THE TERMS OF YOUR CUSTOMER AGREEMENT
COPYRIGHT (C) 2005 AMERICAN CHEMICAL SOCIETY, JAPAN SCIENCE
AND TECHNOLOGY CORPORATION, AND FACHINFORMATIONSZENTRUM KARLSRUHE
```

```
FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Oct 7, 2005 (20051007/UP).
```

```
=> d que 19
L1 ( 1) SEA FILE=HCAPLUS ABB=ON PLU=ON US2003-632197/APPS
L2 SEL PLU=ON L1 1- RN : 98 TERMS
L3 ( 98) SEA FILE=REGISTRY ABB=ON PLU=ON L2
L4 ( 53) SEA FILE=REGISTRY ABB=ON PLU=ON NC5-C6/ES AND L3
L5 ( 9) SEA FILE=REGISTRY ABB=ON PLU=ON C6-C6/ES AND L3
L6 ( 6) SEA FILE=REGISTRY ABB=ON PLU=ON L5 NOT L4
L7 ( 4) SEA FILE=REGISTRY ABB=ON PLU=ON L6 AND (SI/ELS OR BR/ELS)
L8 ( 2) SEA FILE=REGISTRY ABB=ON PLU=ON L6 NOT L7
L9 ( 1) SEA FILE=REGISTRY ABB=ON PLU=ON L8 AND N/ELS
```

```
=> d ide 19
YOU HAVE REQUESTED DATA FROM FILE 'REGISTRY' - CONTINUE? (Y)/N:y
```

```
L9 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2005 ACS on STN
RN 656802-93-6 REGISTRY
ED Entered STN: 02 Mar 2004
CN 2-Naphthalenepropanamide, N, $\beta$ -dihydroxy-6-methoxy- $\alpha$ , $\alpha$ -
dimethyl- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C16 H19 N O4
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL
```



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

1 REFERENCES IN FILE CA (1907 TO DATE)  
 1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> => d his l11

(FILE 'HCAPLUS, TOXCENTER, USPATFULL' ENTERED AT 14:44:48 ON 12 OCT 2005)  
 L11           2 DUP REM L10 (1 DUPLICATE REMOVED)  
               SAVE TEMP L11 HOF197MULS2/A

FILE 'STNGUIDE' ENTERED AT 14:45:55 ON 12 OCT 2005

=> d que l11  
 L1 (           1) SEA FILE=HCAPLUS ABB=ON   PLU=ON  US2003-632197/APPS  
 L2              SEL PLU=ON  L1 1- RN :           98 TERMS  
 L3 (           98) SEA FILE=REGISTRY ABB=ON   PLU=ON  L2  
 L4 (           53) SEA FILE=REGISTRY ABB=ON   PLU=ON  NC5-C6/ES AND L3  
 L5 (           9) SEA FILE=REGISTRY ABB=ON   PLU=ON  C6-C6/ES AND L3  
 L6 (           6) SEA FILE=REGISTRY ABB=ON   PLU=ON  L5 NOT L4  
 L7 (           4) SEA FILE=REGISTRY ABB=ON   PLU=ON  L6 AND (SI/ELS OR BR/ELS)  
 L8 (           2) SEA FILE=REGISTRY ABB=ON   PLU=ON  L6 NOT L7  
 L9             1 SEA FILE=REGISTRY ABB=ON   PLU=ON  L8 AND N/ELS  
 L10          3 SEA L9  
 L11          2 DUP REM L10 (1 DUPLICATE REMOVED)

=> d ibib ed ab hitstr l11 1

YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS, USPATFULL' - CONTINUE? (Y)/N:y

L11 ANSWER 1 OF 2 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 1  
 ACCESSION NUMBER:           2004:120672 HCAPLUS  
 DOCUMENT NUMBER:           140:177322  
 TITLE:                     Hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNF $\alpha$  converting enzyme for use in treatment of diseases  
 INVENTOR(S):              Maduskuie, Thomas P.  
 PATENT ASSIGNEE(S):       Bristol-Myers Squibb Company, USA  
 SOURCE:                   PCT Int. Appl., 81 pp.  
 CODEN:                   PIXXD2  
 DOCUMENT TYPE:           Patent  
 LANGUAGE:                English  
 FAMILY ACC. NUM. COUNT:  1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
-----	-----	-----	-----	-----

WO 2004012663	A2	20040212	WO 2003-US23989	20030731
WO 2004012663	A3	20040708		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004063698	A1	20040401	US 2003-632197	20030731

PRIORITY APPLN. INFO.: MARPAT 140:177322  
 OTHER SOURCE(S):

ED Entered STN: 13 Feb 2004

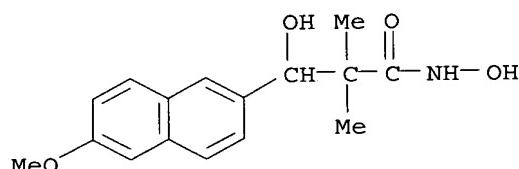
AB MMP or TACE-inhibiting hydroxamic acid derivs. for use in treatment of diseases are disclosed. Thus, 3,N-dihydroxy-2,2-dimethyl-3-[6-(2-methylquinolin-4-ylmethoxy)naphthalen-2-yl]propionamide (I), 4,N-dihydroxy-4-[4-(2-methylquinolin-4-ylmethoxy)phenyl]butyramide (II), N-Hydroxy-2-{2-[4-(2-methylquinolin-4-ylmethoxy)phenyl]tetrahydrofuran-2-yl}acetamide (III), and 3,N-dihydroxy-3-(6-methoxynaphthalen-2-yl)-2,2-dimethylpropionamide (IV) as well as 23 other compds. were synthesized and tested as MMP inhibitors. Some of these compds. inhibited MMPs with Ki's  $\leq 10 \mu\text{M}$ .

IT 656802-93-6P

RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNF $\alpha$  converting enzyme for use in treatment of diseases)

RN 656802-93-6 HCPLUS

CN 2-Naphthalenepropanamide, N, $\beta$ -dihydroxy-6-methoxy- $\alpha$ , $\alpha$ -dimethyl- (9CI) (CA INDEX NAME)



=> d ibib ab hitstr l11 2  
 YOU HAVE REQUESTED DATA FROM FILE 'HCPLUS, USPATFULL' - CONTINUE? (Y)/N:y

L11 ANSWER 2 OF 2 USPATFULL on STN

ACCESSION NUMBER: 2004:83242 USPATFULL  
 TITLE: Hydantoin derivatives as inhibitors of matrix metalloproteinases and/or TNF-alpha converting enzyme  
 INVENTOR(S): Maduskuie, Thomas P., Wilmington, DE, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004063698	A1	20040401
APPLICATION INFO.:	US 2003-632197	A1	20030731 (10)

NUMBER	DATE
PRIORITY INFORMATION:	US 2002-400237P
DOCUMENT TYPE:	20020801 (60)
FILE SEGMENT:	Utility
LEGAL REPRESENTATIVE:	APPLICATION
NUMBER OF CLAIMS:	STEPHEN B. DAVIS, BRISTOL-MYERS SQUIBB COMPANY, PATENT DEPARTMENT, P O BOX 4000, PRINCETON, NJ, 08543-4000
EXEMPLARY CLAIM:	18
LINE COUNT:	3217

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides compounds of Formula (I): ##STR1##

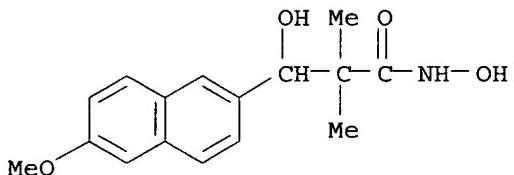
or a stereoisomer or pharmaceutically acceptable salt form thereof,  
 wherein the variables A, R.<sup>1</sup>, R.<sup>2</sup>, R.<sup>3</sup>, R.<sup>4</sup>, Z, U, X, Y,  
 Z.<sup>a</sup>, and n are defined are as defined herein, which are useful as  
 inhibitors of matrix metalloproteinases (MMP) and/or TNF- $\alpha$   
 converting enzyme (TACE), or a combination thereof.

IT 656802-93-6P

(hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or  
 TNF $\alpha$  converting enzyme for use in treatment of diseases)

RN 656802-93-6 USPATFULL

CN 2-Naphthalenepropanamide, N, $\beta$ -dihydroxy-6-methoxy- $\alpha$ , $\alpha$ -  
 dimethyl- (9CI) (CA INDEX NAME)



24

Hoffman 10/632,197

10/13/2005

=> => fil hcpl  
FILE 'HCAPLUS' ENTERED AT 08:31:12 ON 13 OCT 2005  
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.  
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.  
COPYRIGHT (C) 2005 AMERICAN CHEMICAL SOCIETY (ACS)

Copyright of the articles to which records in this database refer is held by the publishers listed in the PUBLISHER (PB) field (available for records published or updated in Chemical Abstracts after December 26, 1996), unless otherwise indicated in the original publications. The CA Lexicon is the copyrighted intellectual property of the American Chemical Society and is provided to assist you in searching databases on STN. Any dissemination, distribution, copying, or storing of this information, without the prior written consent of CAS, is strictly prohibited.

FILE COVERS 1907 - 13 Oct 2005 VOL 143 ISS 16  
FILE LAST UPDATED: 12 Oct 2005 (20051012/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> fil medline  
'MEDLINE' IS NOT A VALID FILE NAME  
SESSION CONTINUES IN FILE 'HCAPLUS'  
Enter "HELP FILE NAMES" at an arrow prompt (>) for a list of files that are available. If you have requested multiple files, you can specify a corrected file name or you can enter "IGNORE" to continue accessing the remaining file names entered.

=> fil medline  
FILE 'MEDLINE' ENTERED AT 08:31:18 ON 13 OCT 2005

FILE LAST UPDATED: 12 OCT 2005 (20051012/UP). FILE COVERS 1950 TO DATE.

On December 19, 2004, the 2005 MeSH terms were loaded.

The MEDLINE reload for 2005 is now available. For details enter HELP RLOAD at an arrow prompt (>). See also:

<http://www.nlm.nih.gov/mesh/>  
[http://www.nlm.nih.gov/pubs/techbull/nd04/nd04\\_mesh.html](http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html)

OLDMEDLINE now back to 1950.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2005 vocabulary.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> fil wpix  
FILE 'WPIX' ENTERED AT 08:31:28 ON 13 OCT 2005  
COPYRIGHT (C) 2005 THE THOMSON CORPORATION

FILE LAST UPDATED: 11 OCT 2005 <20051011/UP>

MOST RECENT DERWENT UPDATE: 200565 <200565/DW>  
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

>>> FOR A COPY OF THE DERWENT WORLD PATENTS INDEX STN USER GUIDE,  
PLEASE VISIT:  
[<<<](http://www.stn-international.de/training_center/patents/stn_guide.pdf)

>>> FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES, SEE  
<http://thomsonderwent.com/coverage/latestupdates/> <<<

>>> FOR INFORMATION ON ALL DERWENT WORLD PATENTS INDEX USER  
GUIDES, PLEASE VISIT:  
<http://thomsonderwent.com/support/userguides/> <<<

>>> NEW! FAST-ALERTING ACCESS TO NEWLY-PUBLISHED PATENT  
DOCUMENTATION NOW AVAILABLE IN DERWENT WORLD PATENTS INDEX  
FIRST VIEW - FILE WPIFV.  
FOR FURTHER DETAILS: [<<<](http://www.thomsonderwent.com/dwpifv)

>>> THE CPI AND EPI MANUAL CODES HAVE BEEN REVISED FROM UPDATE 200501.  
PLEASE CHECK:  
<http://thomsonderwent.com/support/dwpieref/reftools/classification/code-revision/>  
FOR DETAILS. <<<

=> fil embase  
FILE 'EMBASE' ENTERED AT 08:31:32 ON 13 OCT 2005  
Copyright (c) 2005 Elsevier B.V. All rights reserved.

FILE COVERS 1974 TO 6 Oct 2005 (20051006/ED)

EMBASE has been reloaded. Enter HELP RLOAD for details.

This file contains CAS Registry Numbers for easy and accurate  
substance identification.

=> file biosis  
FILE 'BIOSIS' ENTERED AT 08:31:35 ON 13 OCT 2005  
Copyright (c) 2005 The Thomson Corporation

FILE COVERS 1969 TO DATE.  
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT  
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 12 October 2005 (20051012/ED)

FILE RELOADED: 19 October 2003.

=> fil pascal  
FILE 'PASCAL' ENTERED AT 08:31:39 ON 13 OCT 2005  
Any reproduction or dissemination in part or in full,  
by means of any process and on any support whatsoever  
is prohibited without the prior written agreement of INIST-CNRS.  
COPYRIGHT (C) 2005 INIST-CNRS. All rights reserved.

FILE LAST UPDATED: 10 OCT 2005 <20051010/UP>  
FILE COVERS 1977 TO DATE.

>>> SIMULTANEOUS LEFT AND RIGHT TRUNCATION IS AVAILABLE  
IN THE BASIC INDEX (/BI) FIELD <<<

=> fil jicst  
FILE 'JICST-EPLUS' ENTERED AT 08:31:42 ON 13 OCT 2005  
COPYRIGHT (C) 2005 Japan Science and Technology Agency (JST)

FILE COVERS 1985 TO 12 OCT 2005 (20051012/ED)

THE JICST-EPLUS FILE HAS BEEN RELOADED TO REFLECT THE 1999 CONTROLLED TERM (/CT) THESAURUS RELOAD.

=> fil caba  
FILE 'CABA' ENTERED AT 08:31:45 ON 13 OCT 2005  
COPYRIGHT (C) 2005 CAB INTERNATIONAL (CABI)

FILE COVERS 1973 TO 7 Oct 2005 (20051007/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

The CABA file was reloaded 7 December 2003. Enter HELP RLOAD for details.

=> fil cancerlit  
FILE 'CANCERLIT' ENTERED AT 08:31:49 ON 13 OCT 2005

FILE COVERS 1963 TO 15 Nov 2002 (20021115/ED)

On July 28, 2002, CANCERLIT was reloaded. See HELP RLOAD for details.

CANCERLIT thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2002 vocabulary. Enter HELP THESAURUS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> fil drugu  
FILE 'DRUGU' ENTERED AT 08:31:53 ON 13 OCT 2005  
COPYRIGHT (C) 2005 THE THOMSON CORPORATION

FILE LAST UPDATED: 11 OCT 2005 <20051011/UP>  
>>> DERWENT DRUG FILE (SUBSCRIBER) <<<

>>> FILE COVERS 1983 TO DATE <<<  
>>> THESAURUS AVAILABLE IN /CT <<<

=> fil scisearch  
FILE 'SCISEARCH' ENTERED AT 08:31:58 ON 13 OCT 2005  
Copyright (c) 2005 The Thomson Corporation

FILE COVERS 1974 TO 6 Oct 2005 (20051006/ED)

SCISEARCH has been reloaded, see HELP RLOAD for details.

=> fil conf  
FILE 'CONF' ENTERED AT 08:32:00 ON 13 OCT 2005  
COPYRIGHT (c) 2005 FIZ Karlsruhe

FILE LAST UPDATED: 7 OCT 2005 <20051007/UP>  
FILE COVERS 1976 TO DATE.

=> fil confsci

FILE 'CONFSCI' ENTERED AT 08:32:09 ON 13 OCT 2005  
COPYRIGHT (C) 2005 Cambridge Scientific Abstracts (CSA)

FILE COVERS 1973 TO 25 May 2005 (20050525/ED)

=> fil dissabs

FILE 'DISSABS' ENTERED AT 08:32:14 ON 13 OCT 2005  
COPYRIGHT (C) 2005 ProQuest Information and Learning Company; All Rights Reserved.

FILE COVERS 1861 TO 29 SEP 2005 (20050929/ED)

Only fair use as provided by the United States copyright law is permitted. PROQUEST INFORMATION AND LEARNING COMPANY MAKES NO WARRANTY REGARDING THE ACCURACY, COMPLETENESS OR TIMELINESS OF THE LICENSED MATERIALS OR ANY WARRANTY, EXPRESS OR IMPLIED, INCLUDING ANY WARRANTY OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE, AND SHALL NOT BE LIABLE FOR DAMAGES OF ANY KIND OR LOST PROFITS OR OTHER CLAIMS RELATED TO THE LICENSED MATERIALS OR THEIR USE.

=> file stnguide

FILE 'STNGUIDE' ENTERED AT 08:32:16 ON 13 OCT 2005  
USE IS SUBJECT TO THE TERMS OF YOUR CUSTOMER AGREEMENT  
COPYRIGHT (C) 2005 AMERICAN CHEMICAL SOCIETY, JAPAN SCIENCE  
AND TECHNOLOGY CORPORATION, AND FACHINFORMATIONSZENTRUM KARLSRUHE

FILE CONTAINS CURRENT INFORMATION.

LAST RELOADED: Oct 7, 2005 (20051007/UP).

=> d que 120

L11 ( 1) SEA FILE=WPIX ABB=ON PLU=ON (RADLBS/DCN OR RADLCX/DCN OR RADLCZ/DCN OR RADLD1/DCN OR RADLD3/DCN OR RADLD6/DCN OR RADL2W/DCN OR RADL2X/DCN OR RADL2Y/DCN OR RADL2Z/DCN OR RADL3C/DCN OR RADL3E/DCN OR RADL3J/DCN OR RADL3K/DCN OR RADL3W/DCN OR RADL3Y/DCN OR RADL3Z/DCN OR RADL30/DCN OR RADL4D/DCN OR RADL4J/DCN OR RADL40/DCN OR RADL41/DCN OR RADL42/DCN OR RADL47/DCN OR RADL81/DCN OR RADL89/DCN OR 0125-21301/DCN OR 0125-21302/DCN OR 0125-21303/DCN OR 0125-2130 4/DCN OR 0125-21305/DCN OR 0125-21306/DCN OR 0125-21307/DCN OR 0125-21308/DCN OR 0125-21309/DCN OR 0125-21310/DCN OR 0125-2131 1/DCN OR 0125-21312/DCN OR 0125-21313/DCN OR 0125-21314/DCN)

L12 ( 27282) SEA FILE=WPIX ABB=ON PLU=ON ((D621 OR D622) (P) (G011 OR G012 OR G013 OR G014 OR G015 OR G016 OR G221 OR F431 OR F541))/M0,M1 ,M2,M3,M4,M5,M6

L13 ( 328) SEA FILE=WPIX ABB=ON PLU=ON (?HYDANTOI?/BIX OR ?HYDROXAM?/BIX ) (L) (MMP/BIX OR (?MATRIX?/BIX(2A) (?METALLOPROT?/BIX OR (?METALLO/BIX(1W) PROT?/BIX))) OR TNF/BIX OR ((?TUMOR?/BIX OR ?TUMOUR?/BIX) (2A)?NECRO?/BIX) OR TACE/BIX OR (?ALPHA?/BIX(2A) (?CONVERT?/BIX OR ?CONVERS?/BIX)))

L14 ( 40) SEA FILE=WPIX ABB=ON PLU=ON (L11 OR L12) AND L13

L15 ( 3929) SEA FILE=WPIX ABB=ON PLU=ON (MMP/BIX OR (?MATRIX?/BIX(2A) (?METALLOPROT?/BIX OR (?METALLO/BIX(1W) PROT?/BIX))) OR TNF/BIX OR ((?TUMOR?/BIX OR ?TUMOUR?/BIX) (2A)?NECRO?/BIX) OR TACE/BIX OR (?ALPHA?/BIX(2A) (?CONVERT?/BIX OR ?CONVERS?/BIX))) (7A) (?INHIBIT?/BIX OR ?REPRESS?/BIX OR ?SUPRESS?/BIX OR ?DISRUPT?/B IX OR ?INTERRUPT?/BIX OR ?ANTAGON?/BIX OR ?PROHIBIT?/BIX OR ?PREVENT?/BIX OR ?IMPED?/BIX OR ?REDUC?/BIX OR ?DEPRESS?/BIX OR ?BLOCK?/BIX OR STOP?/BIX OR ?RETARD?/BIX OR SLOW?/BIX)

L16 ( 304) SEA FILE=WPIX ABB=ON PLU=ON L15 (L) (?HYDANTOI?/BIX OR ?HYDROXAM?/BIX)

L17 38 SEA FILE=WPIX ABB=ON PLU=ON L14 AND L16

L19 196 SEA FILE=WPIX ABB=ON PLU=ON (?HYDANTOI?/BIX OR ?HYDROXAM?/BIX ) (L) (?QUINOLIN?/BIX)

L20 14 SEA FILE=WPIX ABB=ON PLU=ON L17 AND L19

=> d que 131

L1 QUE ABB=ON PLU=ON ?HYDANTOI? OR ?HYDROXAM?

L6 QUE ABB=ON PLU=ON ?QUINOLIN?

L7 QUE ABB=ON PLU=ON ?PHENYL? OR ?BENZYL? OR ?NAPHTHYL? O R ?NAPHTHENYL? OR ?PYRIDYL? OR ?PYRIDIN? OR ?PYRIMIDYL? O R ?PYRIMIDIN? OR ?BENZENE?

L21 QUE ABB=ON PLU=ON MMP OR (?MATRIX?(2A) (?METALLOPROT? O R (?METALLO(1W) PROT?))) OR TNF OR ((?TUMOR? OR ?TUMOUR?) (2A)?NECRO?) OR TACE OR (?ALPHA?(2A) (?CONVERT? OR ?CONVERS ?))

L23 15230 SEA FILE=MEDLINE ABB=ON PLU=ON HYDANTOINS+PFT,NT/CT

L24 485 SEA FILE=MEDLINE ABB=ON PLU=ON L23 (L) AA

L25 3 SEA FILE=MEDLINE ABB=ON PLU=ON L24 AND L21

L26 367 SEA FILE=MEDLINE ABB=ON PLU=ON L1 (L) L21

L27 970 SEA FILE=MEDLINE ABB=ON PLU=ON L1 (10A) (L6 OR L7)

L28 34 SEA FILE=MEDLINE ABB=ON PLU=ON L26 AND L27

L29 14 SEA FILE=MEDLINE ABB=ON PLU=ON L1 (7A) L6

L30 4 SEA FILE=MEDLINE ABB=ON PLU=ON L28 AND L29

L31 7 SEA FILE=MEDLINE ABB=ON PLU=ON L25 OR L30

=> d que 139

L1 QUE ABB=ON PLU=ON ?HYDANTOI? OR ?HYDROXAM?

L6           QUE ABB=ON PLU=ON ?QUINOLIN?  
 L7           QUE ABB=ON PLU=ON ?PHENYL? OR ?BENZYL? OR ?NAPHTHYL? O  
              R ?NAPHTHENYL? OR ?PYRIDYL? OR ?PYRIDIN? OR ?PYRIMIDYL? O  
              R ?PYRIMIDIN? OR ?BENZENE?  
 L21          QUE ABB=ON PLU=ON MMP OR (?MATRIX?(2A) (?METALLOPROT? O  
              R (?METALLO(1W) PROT?))) OR TNF OR ((?TUMOR? OR ?TUMOUR?) (2A) ?NECRO?) OR TACE OR (?ALPHA?(2A) (?CONVERT? OR ?CONVERS?))  
 L32          50409 SEA FILE=EMBASE ABB=ON PLU=ON "HYDANTOIN DERIVATIVE"+PFT,NT/C  
              T  
 L33          187 SEA FILE=EMBASE ABB=ON PLU=ON L32 AND L21  
 L36          391 SEA FILE=EMBASE ABB=ON PLU=ON L1 (L) L21  
 L37          17 SEA FILE=EMBASE ABB=ON PLU=ON L33 AND L36  
 L38          11 SEA FILE=EMBASE ABB=ON PLU=ON L37 AND (L6 OR L7)  
 L39          17 SEA FILE=EMBASE ABB=ON PLU=ON L37 OR L38

=> d his 147

(FILE 'BIOSIS, PASCAL, JICST-EPLUS, CABA, CANCERLIT, DRUGU, SCISEARCH'  
 ENTERED AT 08:16:50 ON 13 OCT 2005)  
 L47          53 DUP REM L46 (21 DUPLICATES REMOVED)

=> d que 147

L1           QUE ABB=ON PLU=ON ?HYDANTOI? OR ?HYDROXAM?  
 L6           QUE ABB=ON PLU=ON ?QUINOLIN?  
 L7           QUE ABB=ON PLU=ON ?PHENYL? OR ?BENZYL? OR ?NAPHTHYL? O  
              R ?NAPHTHENYL? OR ?PYRIDYL? OR ?PYRIDIN? OR ?PYRIMIDYL? O  
              R ?PYRIMIDIN? OR ?BENZENE?  
 L21          QUE ABB=ON PLU=ON MMP OR (?MATRIX?(2A) (?METALLOPROT? O  
              R (?METALLO(1W) PROT?))) OR TNF OR ((?TUMOR? OR ?TUMOUR?) (2A) ?NECRO?) OR TACE OR (?ALPHA?(2A) (?CONVERT? OR ?CONVERS?))  
 L40          6407 SEA L1 (7A) (L6 OR L7)  
 L41          20700 SEA L1/TI, IT, CC, CT, ST, STP  
 L42          4900 SEA L40 AND L41  
 L43          1538 SEA L1 (L) L21  
 L44          87 SEA L42 AND L43  
 L45          269429 SEA L21/TI, IT, CC, CT, ST, STP  
 L46          74 SEA L44 AND L45  
 L47          53 DUP REM L46 (21 DUPLICATES REMOVED)

=> dup rem 120 131 139 147

FILE 'WPIX' ENTERED AT 08:33:16 ON 13 OCT 2005  
 COPYRIGHT (C) 2005 THE THOMSON CORPORATION

FILE 'MEDLINE' ENTERED AT 08:33:16 ON 13 OCT 2005

FILE 'EMBASE' ENTERED AT 08:33:16 ON 13 OCT 2005  
 Copyright (c) 2005 Elsevier B.V. All rights reserved.

FILE 'BIOSIS' ENTERED AT 08:33:16 ON 13 OCT 2005  
 Copyright (c) 2005 The Thomson Corporation

FILE 'PASCAL' ENTERED AT 08:33:16 ON 13 OCT 2005  
 Any reproduction or dissemination in part or in full,  
 by means of any process and on any support whatsoever  
 is prohibited without the prior written agreement of INIST-CNRS.  
 COPYRIGHT (C) 2005 INIST-CNRS. All rights reserved.

FILE 'CANCERLIT' ENTERED AT 08:33:16 ON 13 OCT 2005

FILE 'DRUGU' ENTERED AT 08:33:16 ON 13 OCT 2005

COPYRIGHT (C) 2005 THE THOMSON CORPORATION

FILE 'SCISEARCH' ENTERED AT 08:33:16 ON 13 OCT 2005

Copyright (c) 2005 The Thomson Corporation

PROCESSING COMPLETED FOR L20

PROCESSING COMPLETED FOR L31

PROCESSING COMPLETED FOR L39

PROCESSING COMPLETED FOR L47

L51 85 DUP REM L20 L31 L39 L47 (6 DUPLICATES REMOVED)

ANSWERS '1-14' FROM FILE WPIX

ANSWERS '15-21' FROM FILE MEDLINE

ANSWERS '22-37' FROM FILE EMBASE

ANSWERS '38-53' FROM FILE BIOSIS

ANSWERS '54-75' FROM FILE PASCAL

ANSWER '76' FROM FILE CANCERLIT

ANSWERS '77-78' FROM FILE DRUGU

ANSWERS '79-85' FROM FILE SCISEARCH

=> file stnguide

FILE '/STNGUIDE!' ENTERED AT 08:33:24 ON 13 OCT 2005

USE IS SUBJECT TO THE TERMS OF YOUR CUSTOMER AGREEMENT

COPYRIGHT (C) 2005 AMERICAN CHEMICAL SOCIETY, JAPAN SCIENCE

AND TECHNOLOGY CORPORATION, AND FACHINFORMATIONSZENTRUM KARLSRUHE

FILE CONTAINS CURRENT INFORMATION.

LAST RELOADED: Oct 7, 2005 (20051007/UP).

=> d iall abeq tech abex

YOU HAVE REQUESTED DATA FROM FILE 'WPIX, MEDLINE, EMBASE, BIOSIS, PASCAL, CANCERLIT, DRUGU, SCISEARCH' - CONTINUE? (Y)/N:y

L51 ANSWER 1 OF 85 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN  
 ACCESSION NUMBER: 2005-630225 [64] WPIX  
 DOC. NO. CPI: C2005-189027  
 TITLE: New substituted hydroxamic acid derivatives are matrix metalloproteinase inhibitors and tumor necrosis factor inhibitors useful for treating e.g. inflammatory, infectious, immunological and malignant diseases.  
 DERWENT CLASS: B03  
 INVENTOR(S): JAIN, M R; LOHRAY, B B; LOHRAY, V B; THOMBARE, P S  
 PATENT ASSIGNEE(S): (CADI-N) CADILA HEALTHCARE LTD  
 COUNTRY COUNT: 108  
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN	IPC
WO 2005077937	A1	20050825 (200564)*	EN	43	C07D401-12		
RW:	AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IS IT KE LS LT LU MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW						
W:	AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW						

#### APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2005077937	A1	WO 2005-IN10	20050107

PRIORITY APPLN. INFO: IN 2004-MU22 20040109

INT. PATENT CLASSIF.:

MAIN:	C07D401-12
SECONDARY:	A61K031-4025; A61K031-4709; A61P029-00; C07D405-14;
	C07D409-14

#### BASIC ABSTRACT:

WO2005077937 A UPAB: 20051006

NOVELTY - Substituted hydroxamic acid derivatives, or their salts, solvates, stereoisomers or tautomers are new.

DETAILED DESCRIPTION - Substituted hydroxamic acid derivatives of formula (I), or their salts, solvates, stereoisomers or tautomers are new.

A = COR1, COOH, CH<sub>2</sub>COOH, CONHOH, CONHOR1, N(OH)COR1, C(=NOR1)NHR1, SH, CH<sub>2</sub>SH, SO<sub>2</sub>NHR1 or S(=NH)2R1;

R1 = linear or branched 1-8C alkyl, 3-7C cycloalkyl, acyl, aryl, aralkyl, alkylamino carbonyl, (hetero)arylamino carbonyl, (hetero)aralkylamino carbonyl or heterocyclyl aminocarbonyl (all optionally substituted by T) or H;

R2 and R3 = linear or branched 1-8C alkyl, 3-7C cycloalkyl, acyl, 3-7C cycloalkyl, aryl, aralkyl, aralkyl, heteroaryl, heterocycle (all

optionally substituted by T), H, or halo;

X = T1;

T1 = 3-13C carbocyclic residue (optionally substituted by T) or 5 - 14-membered heterocyclic group containing 1 - 4 heteroatoms selected from N, O and S;

Z = 3-13C carbocyclic residue (substituted by alkenyl, alkynyl, alkoxy alkyl (all optionally substituted), (CH<sub>2</sub>)<sub>r</sub>- (3-6C) cycloalkyl, (CH<sub>2</sub>)<sub>r</sub>-cycloalkenyl, (CH<sub>2</sub>)<sub>r</sub>-phenyl, or (CH<sub>2</sub>)<sub>r</sub>-3 - 14-membered heterocycle comprising 1 - 4 heteroatoms selected from N, O and S) or 5 - 14-membered heterocyclic system containing 1 - 4 N, O or S;

n = 1 - 2;

r = 0 - 6;

Y = (CR'Rx)p, O(CR'Rx)p, (CR'Rx)pO, C(O)(CR'Rx)p, (CR'Rx)C(O), NR'(CR'Rx)p, NR'NRx, (CR'Rx)pNR', NR'C(O)(CR'Rx)p, CONR'(CR'Rx)p, (CR'Rx)pNR'C(O), (CR'Rx)pNR'C(O), (CR'R')pC(O)NR', NR'CONR', (CR'Rx)pS(O)q, or S(O)q(CR'Rx)p;

R4 = H, SR', halogen, NR'Rx, OR', CN, NO<sub>2</sub>, 1-10C alkyl-Ra, 2-10C alkenyl-Ra, 2-10C alkynyl-Ra, (CR'Rx)p-Ra, O(CR'Rx)pRa, (CR'Rx)pO(CR'Rx)pRa, (CR'Rx)pNR'(CR'Rx)pRa, (CR'Rx)pC(O)O(CR'Ra)pRa, (CR'Rx)pOC(O)(CR'Rx)pRa, (CR'Rx)pC(O)NR'(CR'Rx)pRa, (CR'Rx)pNR'C(O)(CR'Rx)pRa, (CR'Rx)pC(O)NR'(CR'Rx)pRa, (CR'Rx)pS(O)q(CR'Rx)pRa, (CR'Rx)pS(O)qNR'C(CR'Rx)pRa, (CR'Rx)pNR'S(O)q(CR'Rx)pRa, (CR'Rx)pOC(O)NR'(CR'Rx)pRa, or (CR'Rx)pNR'C(O)O(CR'Rx)pRa;

p and q = 0 - 2;

R' and Rx = T2;

T2 = linear or branched 1-6C alkyl, 1-6C alkenyl, 1-6C alkynyl (all optionally substituted), H or alkyl;

Ra = halogen or T2; and

T = a substituent.

An INDEPENDENT CLAIM is included for preparation of (I).

ACTIVITY - Antiinflammatory; Antimicrobial; Antiarthritic; Antirheumatic; Antiulcer; Vulnerary; Osteopathic; Gastrointestinal-Gen.; Cytostatic; Respiratory-Gen.; Antimalarial; Antiasthmatic; Neuroprotective; Nootropic; Immunosuppressive; Immunomodulator; Antiallergic; Antibacterial; Vasotropic; Dermatological; Antiarteriosclerotic; Cardiant; Cerebroprotective; Vulnerary; Anticonvulsant; Antiparkinsonian; Antimigraine; Antidepressant; Analgesic; Anti-HIV; Ophthalmological.

MECHANISM OF ACTION - Matrix degrading metalloproteinase (MMP) inhibitor; Tumor necrosis factor- alpha (TNF- alpha ) inhibitor; Tumor necrosis factor- alpha converting enzyme (TACE) inhibitor; Aggrecanase inhibitor. 2-(3-Amino-3-(4-(2-isopropoxymethyl-quinolin-4-ylmethoxy)-phenyl)-2-oxo-pyrrolidin-1-yl)-4-methyl-pentanoic acid hydroxyamide (a) was tested for TNF- alpha inhibitory activity using rat whole blood assay. Rats were anaesthetized and blood (6 - 8 ml) was collected in a tube containing heparin (100 IU/ml). Blood sample (500 mu l) was incubated with (a) (10 mu M) for 15 minutes at 37 deg. C. LPS (1 mu g/ml) was added and the mixture was further incubated for 5 hours at 37 deg. C. The reaction was terminated by placing the sample over ice for 15 minutes at 4 deg. C. The plasma was collected and TNF- alpha level was estimated by ELISA method. The % inhibition at 10 mu M dose of (a) was 94%.

USE - In the preparation of pharmaceutical composition and in the manufacture of medicament for treatment or prophylaxis of inflammatory, infectious, immunological and malignant diseases in a mammal e.g. human; for treating diseases associated with excess of tumor necrosis factor- alpha production or secretion (claimed) such as

arthritis (e.g. osteoarthritis, rheumatoid arthritis), tissue ulceration (e.g. corneal, epidermal and gastric ulceration); abnormal wound healing; periodontal disease; bone disease (e.g. osteoporosis, Paget's disease), tumor metastasis, inflammatory bowel disease, Crohn's disease, emphysema, malaria, acute respiratory distress syndrome, asthma, chronic obstructive pulmonary disease, Alzheimer's disease, organ transplant toxicity, cachexia, allergic reaction, allergic contact hypersensitivity, cancer (such as solid tumor including colon cancer, breast cancer, lung cancer and prostate cancer and hematopoietic malignancies including leukemia and lymphomas), mycobacterial infection, meningitis, graft rejection, restenosis, epidermolysis bullosa, loosening of artificial joint implants, atherosclerosis (including atherosclerotic plaque rupture), aortic aneurysm (including abdominal aortic aneurysm and brain aortic aneurysm), congestive heart failure, myocardial infarction, stroke, cerebral ischemia, head trauma, spinal cord injury, neuro-degenerative disorders, autoimmune disorders, Huntington's disease, Parkinson's disease, migraine, depression, hyperoxic alveolar injury, peripheral neuropathy, pain, cerebral amyloid angiopathy, nootropic or cognition enhancement, amyotrophic lateral sclerosis, multiple sclerosis, ocular angiogenesis, corneal injury, macular degeneration, abnormal wound healing, burns, diabetes, corneal scarring, scleritis, AIDS, sepsis and septic shock.

**ADVANTAGE** - The compounds are potent **matrix metalloproteinase (MMP)**, aggrecanase and **tumor necrosis factor inhibitors**. The compound exhibits enhanced activities without toxic effects or with reduced toxic effects.

Dwg.0/0

FILE SEGMENT: CPI

FIELD AVAILABILITY: AB; GI; DCN

MANUAL CODES: CPI: B06-H; B07-H; B14-A01; B14-A02; B14-A03B; B14-C01; B14-C03; B14-C09; B14-D03; B14-E08; B14-E10C1; B14-E11B; B14-F01B; B14-F01G; B14-F02C; B14-F02D1; B14-F07; B14-G01B; B14-G02A; B14-G02C; B14-G02D; B14-H01; B14-H01B; B14-J01A1; B14-J01A3; B14-J01A4; B14-K01; B14-K01F; B14-N01; B14-N03; B14-N06B; B14-N16; B14-N17B; B14-S04; B14-S06

TECH UPTX: 20051006

**TECHNOLOGY FOCUS - ORGANIC CHEMISTRY** - Preparation (claimed): Preparation of (I) involves:

- (1) process A: converting a disubstituted pyrrolidine-2-one derivative of formula (II) to a corresponding ester of formula (III); and converting (III) to hydroxamide derivative of formula (I) (where A is CONHOH, X-Y-Z is phenyl (substituted by OCH<sub>2</sub>Z on 4-position));
- (2) process B: optionally converting (III) to 3-substituted amine derivative of formula (IV); and converting (IV) to hydroxamide derivative of formula (I) (where A is CONHOH, R<sub>4</sub> is NH<sub>2</sub>, X-Y-Z is phenyl (substituted on 4-position by OCH<sub>2</sub>-Z));
- (3) process C: optionally converting (III) to hydroxamic acid of formula (I) (where A is COOH, X-Y-Z is phenyl (substituted on 4-position by OCH<sub>2</sub>-Z)); and
- (4) process D: optionally converting (IV) to hydroxamic acid of formula (I) (where A is COOH, R<sub>4</sub> is NH<sub>2</sub>, X-Y-Z is phenyl (substituted on 4-position by OCH<sub>2</sub>Z)).

ABEX UPTX: 20051006

**SPECIFIC COMPOUNDS** - 37 Compounds are specifically claimed as (I) e.g. 2-(3-amino-3-(4-(2-isopropoxymethyl-quinolin-4-ylmethoxy)-phenyl)-2-oxo-pyrrolidin-1-yl)-4-methyl-pentanoic acid hydroxyamide.

**ADMINISTRATION** - (I) Is administered in the form of tablets, pills, capsules, powder, granules, syrup, solution or suspension (claimed) orally. No dosage given.

EXAMPLE - To a solution of 2-(3-tert-butoxycarbonylamino-3-(4-hydroxy-phenyl)-2-oxo-pyrrolidin-1-yl)-4-methyl-pentanoic acid methyl ester (2.0 g), (2-methoxymethyl-quinoline-4-yl)-methanol (1.06 g) and triphenylphosphine (1.37 g) in dichloromethane (20 ml) at 0degreesC was added diisopropyl azodicarboxylate (DIAD) (1.44 g). The mixture was stirred at 25 - 30degreesC for 24 hours and then quenched with water (20 ml) and worked up to give 2-(3-tert-butoxycarbonylamino-3-(4-(2-methoxymethyl-quinoline-4-ylmethoxy)-phenyl)-2-oxo-pyrrolidin-1-yl)-4-methyl-pentanoic acid methyl ester (1.8 g) (A). To a solution of (A) (1.8 g) in dichloromethane (10 ml) at 0degreesC was added trifluoroacetic acid (3.38 g) dropwise. The mixture was stirred at 25 - 30degreesC for 4 hours. Water (10 ml) was added to the mixture, the pH of the mixture was adjusted to 10 by adding 10% aqueous sodium bicarbonate solution and worked up to give 2-(3-amino-3-(4-(2-methoxymethyl-quinolin-4-ylmethoxy)phenyl)-2-oxo-pyrrolidin-1-yl)-4-methyl-pentanoic acid methyl ester (1.4 g) (B). To a hot solution of hydroxylamine hydrochloride (3.83 g) in methanol (30 ml) was added a solution of sodium hydroxide (3.31 g) in methanol (30 ml). The mixture was kept under stirring at 25 - 30degreesC for 30 minutes and then cooled to 5 - 10degreesC, filtered and freshly prepared solution of the hydroxylamine was added to (B) (1.4 g) in methanol (10 ml) at 5 - 10degreesC. The mixture was stirred at 25 - 30degreesC for 2 hours, acidified to pH 6.0 - 6.5 with 1N hydrochloride. The hydroxamic acid was precipitated out to give 2-(3-amino-3-(4-(2-methoxymethyl-quinolin-4-ylmethoxy)-phenyl)-2-oxo-pyrrolidin-1-yl)-4-methyl-pentanoic acid hydroxyamide (1.0 g, 69.5% yield).

DEFINITIONS - Preferred Definitions:

Z=quinolinyl, pyrimidinyl or quinazolinyl; and  
T=OH, oxo, halogen, thio, nitro, amino, cyano, formyl, alkyl, haloalkyl, per-haloalkyl, alkoxy, haloalkoxy, per-haloalkoxy, alkenyl, alkynyl, cycloalkenyl, bicycloalkyl, bicycloalkenyl, alkoxy, alkenoxy, cycloalkoxy, aryloxy, heterocyclyl, (hetero)aryl, (hetero)cycloalkyl, (hetero)aralkyl, heteroaryloxy, (hetero)aralkoxy, heterocyclyloxy, heterocyclylalkoxy, heterocyclylalkoxyacyl, acyl, acyloxy, acylamino, mono or di-substituted amino, arylamino, aralkylamino, carboxylic acid and its derivatives such as esters and amides, carbonylamino, hydroxyalkyl, aminoalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, arylthio, alkylsulfonylamino, aminocarbonylamino, alkylaminocarbonylamino, alkoxyamino, hydroxyl amino, sulfonyloxy, alkylsulfonyloxy, alkoxycoxy carbonylamino, aryloxycarbonylamino, aralkyloxycarbonylamino, sulfenyl derivatives, sulfonyl derivatives, sulfonic acid or its derivative.

=> d iall abeq tech abex 2-14

YOU HAVE REQUESTED DATA FROM FILE 'WPIX, MEDLINE, EMBASE, BIOSIS, PASCAL, CANCERLIT, DRUGU, SCISEARCH' - CONTINUE? (Y)/N:Y

L51 ANSWER 2 OF 85 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN

ACCESSION NUMBER: 2004-594142 [57] WPIX

DOC. NO. CPI: C2004-216155

TITLE: New sulfonyl hydroxamic acid derivatives are soluble human cluster differentiation-23 inhibitors useful to treat or prevent e.g. autoimmune, allergic and inflammatory diseases.

DERWENT CLASS: B05

INVENTOR(S): BRUTON, G

PATENT ASSIGNEE(S) : (GLAX) GLAXO GROUP LTD  
 COUNTRY COUNT: 108  
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN	IPC
<hr/>							
WO 2004067502	A1	20040812 (200457)*	EN	29	C07C317-44		

RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE  
 LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW  
 W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE  
 DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG  
 KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ  
 OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG  
 US UZ VC VN YU ZA ZM ZW

## APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2004067502	A1	WO 2004-EP954	20040130

PRIORITY APPLN. INFO: GB 2003-2431 20030130

INT. PATENT CLASSIF.:

MAIN: C07C317-44

SECONDARY: A61K031-4375; A61P037-00; C07D215-12

## BASIC ABSTRACT:

WO2004067502 A UPAB: 20040907

NOVELTY - Sulfonyl **hydroxamic** acid derivatives (I) or their isomers are new.

DETAILED DESCRIPTION - Sulfonyl **hydroxamic** acid derivatives of formula (I) or their isomers are new.

R = H, alkyl, alkoxy, alkenyl, alkynyl, (hetero)aryl or heterocyclyl; and

R1 = (hetero)bicyclyl.

INDEPENDENT CLAIMS are also included for

- (1) a thioamine derivative of formula (II);
- (2) a thiohydroxylamine derivative of formula (III);
- (3) acid derivative of formula (VIII); and
- (4) preparation of (I).

P = protecting group.

ACTIVITY - Immunosuppressive; Antiallergic; Antiinflammatory; Antiasthmatic; Ophthalmological; Dermatological.

MECHANISM OF ACTION - Soluble human cluster differentiation-23 (S-CD23) inhibitor; Matrix metalloprotease inhibitor; Collagenase inhibitor.

The ability of (I) to inhibit S-CD23 was assessed using plasma membranes from RPMI 8866 cells, human Epstein-Barr virus transformed B-cell lines expressing high levels of CD23. The results showed that median inhibitor concentration (IC50) value of N-hydroxy-2-phenyl-3-(3-quinolin-3-ylmethanesulfonyl)-propionamide was 0.01 micro M.

USE - (I) is useful in the treatment or prevention of disorders in which the overproduction of s-CD23 is implicated (claimed) such as autoimmune diseases, allergic diseases (asthma, rhinitis, allergic conjunctivitis, eczema, atopic dermatitis and anaphylaxis) and inflammatory diseases.

Dwg.0/0

FILE SEGMENT: CPI

FIELD AVAILABILITY: AB; GI; DCN

MANUAL CODES: CPI: B06-D02; B10-A09A; B14-D07C; B14-G02; B14-G02A;

B14-K01; B14-K01A; B14-N03; B14-N17

TECH UPTX: 20040907  
 TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation (claimed): Preparation of (I) comprises either:  
 (1) deprotection of (II);  
 (2) oxidation of (III);  
 (3) conversion of (I) to another compound of (I); and  
 (4) reaction of (VIII) with a hydroxylamine or its salt.

ABEX UPTX: 20040907  
 SPECIFIC COMPOUNDS - 2 compounds (I) are specifically claimed e.g.  
 N-hydroxy-2-phenyl-3-(3-quinolin-3-ylmethanesulfonyl)-propionamide (Ia).

ADMINISTRATION - Administration of (I) is 1 mg-1 g, orally, parenterally, sublingually, transdermally or by inhalation.

EXAMPLE - A suspension of 2-phenyl-3-(3-quinolylmethanesulfonyl)-propionic acid hydrochloride (30 mg) in dichloromethane (5 ml) was treated with oxalyl chloride (0.5 ml) and dimethyl formamide (1 drop). After 1 hour the mixture was evaporated and the resulting solid suspended in dichloromethane (5 ml) and O-trimethylsilylhydroxylamine (0.5 ml) added. The reaction mixture was worked up to give N-hydroxy-2-phenyl-3-(3-quinolin-3-ylmethanesulfonyl)-propionamide (Ia).

DEFINITIONS - Preferred Definitions:

R = aryl or alkoxy (preferably phenyl or propyloxy); and

R<sub>1</sub> = heterobicycyl (preferably quinoline).

L51 ANSWER 3 OF 85 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN

ACCESSION NUMBER: 2004-295066 [27] WPIX

CROSS REFERENCE: 2004-283028 [26]

DOC. NO. CPI: C2004-112879

TITLE: New hydantoin derivatives, useful for treatment of e.g. inflammatory diseases, autoimmune diseases and allergic/atopic diseases, are tumor necrosis factor alpha converting enzyme inhibitors.

DERWENT CLASS: B02 B03

INVENTOR(S): BURROWS, J N; TUCKER, H

PATENT ASSIGNEE(S): (ASTR) ASTRAZENECA AB; (ASTR) ASTRAZENECA UK LTD

COUNTRY COUNT: 106

PATENT INFORMATION:

PATENT NO	KIND DATE	WEEK	LA	PG	MAIN IPC
<hr/>					
WO 2004024721	A1 20040325 (200427)* EN	67	C07D401-14		
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS					
LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK					
DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR					
KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG PH					
PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC					
VN YU ZA ZM ZW					
AU 2003263347	A1 20040430 (200462)			C07D401-14	
NO 2005001788	A 20050613 (200545)			C07D401-14	
EP 1551826	A1 20050713 (200546) EN			C07D401-14	
R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LT LU LV					
MC MK NL PT RO SE SI SK TR					
BR 2003014275	A 20050809 (200554)			C07D401-14	

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2004024721	A1	WO 2003-GB3914	20030909
AU 2003263347	A1	AU 2003-263347	20030909
NO 2005001788	A	WO 2003-GB3914	20030909
		NO 2005-1788	20050412
EP 1551826	A1	EP 2003-795075	20030909
		WO 2003-GB3914	20030909
BR 2003014275	A	BR 2003-14275	20030909
		WO 2003-GB3914	20030909

## FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2003263347	A1 Based on	WO 2004024721
EP 1551826	A1 Based on	WO 2004024721
BR 2003014275	A Based on	WO 2004024721

PRIORITY APPLN. INFO: GB 2002-21246 20020913

## INT. PATENT CLASSIF.:

MAIN: C07D401-14

SECONDARY: A61K031-4166; A61K031-47; A61P043-00; C07D403-06

## BASIC ABSTRACT:

WO2004024721 A UPAB: 20050823

NOVELTY - **Hydantoin** derivatives (I) are new.DETAILED DESCRIPTION - **Hydantoin** derivatives of formula (I) and their salts are new.

Y1, Y2 = O;

Z1 = NR8, O or S;

n, t = 0 or 1;

W1 = CR1R2 or a bond;

V1 = a group of formula (a);

B1 = 2-4C alkenyl, 2-4C alkynyl, 5-6C cycloalkenyl (all optionally substituted by halo or R9), (hetero)aryl, heterocyclyl (optionally substituted by NO2, CF3, OCF3, halo, CN, 1-4C alkyl (optionally substituted by R9 or 1-4C alkoxy or one or more halo), 3-6C cycloalkyl (optionally substituted by R9 or one or more halo), (hetero)aryl (optionally substituted by halo or 1-4C alkyl), heterocyclyl (optionally substituted by 1-4C alkyl), S(O)mR11, SO2NR9R10, NR9SO2R11, NHCONR9R10, OR9, NR9R10, CONR9R10 and/or NR9COR10); or

B1 = 2-4C alkenyl or 2-4C alkynyl (optionally substituted by 1-4C alkyl, 3-6C cycloalkyl, (hetero)aryl, heterocyclyl (optionally substituted by one or more halo, nitro, CN, CF3, OCF3, CONHR9, CONR9R10, SO2R11, SO2NR9R10, NR9SO2R11, 1-4C alkyl or 1-4C alkoxy));

m = 0-2;

R1, R2 = 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl, 3-6C cycloalkyl or 5-6C cycloalkenyl (all optionally substituted by halo, CN, OH or 1-4C alkoxy) or H;

R3-R6 = 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl, 3-6C cycloalkyl, 5-6C cycloalkenyl, (hetero)aryl, heterocyclyl (optionally substituted by halo, nitro, CN, CF3, OCF3, 1-4C alkyl, 2-4C alkenyl, 2-4C alkynyl, 3-6C cycloalkyl (optionally substituted by one or more R17), (hetero)aryl (optionally substituted by one or more R17), heterocyclyl, OR18, S(O)mR19, COR19, CO2R18, CONR18R20, NR16COR18, SO2NR18R20 and/or NR16SO2R16) or H; or

CR1R3, CR3R4, CR3R5, CR5R6 = saturated 3-7-membered ring optionally containing 1 or 2 heteroatoms NH, O, S, SO or SO2, where the ring is optionally substituted on C by 1-4C alkyl, F or 1-3C alkoxy and/or N by 1-4C alkyl, CO(1-3C alkyl) or SO2(1-3C alkyl);

R7 = H, 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl, heteroalkyl, 3-7C cycloalkyl, (hetero)aryl or heterocyclyl (optionally substituted by halo, 1-4C alkyl, 1-4C alkoxy, 3-7C cycloalkyl, heterocyclyl, (hetero)aryl or heteroalkyl)) (all optionally substituted by halo, CN, 1-4C alkyl, nitro, halo(1-4C alkyl), heteroalkyl, (hetero)aryl, hydroxy(1-4C alkyl), 3-7C cycloalkyl, heterocyclyl, 1-4C alkoxy(1-4C alkyl), halo(1-4C alkoxy)(1-4C alkyl), CO(1-4C alkyl), OR12, CO2R21, S(O)mR25, NR21COR21, CONR21R22 and/or NHCOR21R22); or

CR3R7, (CR5R6)n = saturated 5-7 membered ring optionally containing a hetero atom of NH, O, S, SO or SO<sub>2</sub>, where the ring is optionally substituted on C by 1-4C alkyl, F or 1-3C alkoxy and/or N by 1-4C alkyl, CO(1-3C alkyl) or SO<sub>2</sub>(1-3C alkyl);

R8 = H or CH<sub>3</sub>;

R9, R10, R12, R13 = H, 1-6C alkyl or 3-6C cycloalkyl; or

NR9R10 = heterocyclic 4-7 membered ring;

R11 = 1-6C alkyl or 3-6C cycloalkyl;

R14 = H, CN, NR23R24 or 1-4C alkyl (optionally substituted by halo, OR23 or NR23R24);

R16, R23, R24 = H or 1-6C alkyl;

R17 = halo, 1-6C alkyl, 3-6C cycloalkyl or 1-6C alkoxy;

R19, R25 = 1-6C alkyl, 3-6C cycloalkyl, 5-6C cycloalkenyl, saturated heterocyclyl, (hetero)aryl, aryl(1-4C alkyl) or heteroaryl(1-4C alkyl) (all optionally substituted by one or more halo);

R18 = 1-6C alkyl, 3-6C cycloalkyl, 5-6C cycloalkenyl, saturated heterocyclyl, (hetero)aryl, aryl(1-4C alkyl), heteroaryl(1-4C alkyl) (optionally substituted by one or more halo) or H;

R20 = H, 1-6C alkyl or 3-6C cycloalkyl; or

NR18R20 = heterocyclic 4-7 membered ring; and

R21, R22 = H, 1-4C alkyl, halo(1-4C alkyl), aryl or aryl(1-4C alkyl). ACTIVITY - Antiinflammatory; Immunosuppressive; Antiallergic;

Cardiovascular-Gen.; Vasotropic; Cytostatic; Respiratory-Gen.;

Antiasthmatic; Antiarthritic; Antirheumatic; Antipsoriatic;

Dermatological.

MECHANISM OF ACTION - Metalloproteinase inhibitor;

Tumor Necrosis Factor- alpha

converting enzyme (TACE) inhibitor.

(I) were assessed for TACE inhibitory activity using partially purified enzyme assay. The results showed that MIC value of 5-(3-methyl-3-(4-(2-methylquinolin-4-ylmethoxy)phenyl)-2-oxopyrrolidin-1-ylmethyl)-5-phenylimidazolidine-2,4-dione was 130 nM.

USE - (I) are useful in the manufacture of medicament for the treatment of inflammatory diseases, autoimmune diseases, allergic/atopic diseases, transplant rejection, graft versus host disease, cardiovascular disease, reperfusion injury and malignancy in a warm-blooded animal such as man (claimed), respiratory disorders such as asthma or chronic obstructive pulmonary disease, rheumatoid arthritis, Crohn's disease and psoriasis.

ADVANTAGE - (I) have good potency and/or pharmacokinetic properties.

Dwg.0/0

FILE SEGMENT: CPI

FIELD AVAILABILITY: AB; GI; DCN

MANUAL CODES: CPI: B06-H; B07-H; B14-C03; B14-C09B; B14-D07C; B14-E10C; B14-F01; B14-F02; B14-F05; B14-G02A; B14-G02C; B14-G02D; B14-H01; B14-K01; B14-K01A; B14-N17C

TECH UPTX: 20040426

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: Claimed preparation of (I) comprises conversion of a ketone or aldehyde of formula (II) into (I), if necessary

- (a) converting (I) into another compound of formula (I);
- (b) removing any protecting groups; and

(c) forming a pharmaceutically acceptable salt or in vivo hydrolyzable ester.

ABEX UPTX: 20040426

SPECIFIC COMPOUNDS - 14 compounds (I) are specifically disclosed e.g. 5-(3-methyl-3-(4-(2-methylquinolin-4-ylmethoxy)phenyl)-2-oxopyrrolidin-1-ylmethyl)-5-phenylimidazolidine-2,4-dione of formula (Ia).

ADMINISTRATION - Administration of (I) is 0.5-0.75 (preferably 0.5-30) mg/kg/day, orally, parenterally, topically, rectally or by inhalation. EXAMPLE - 1-(2-Hydroxy-2-phenylethyl)-3-methyl-3-(4-(2-methylquinolin-4-ylmethoxy)phenyl)pyrrolidin-2-one (120 mg) was dissolved in dichloromethane (4 ml). 4-Methylmorpholine N-oxide (53 mg) and 4A molecular sieves (300 mg) were added. The reaction was stirred for 10 minutes before addition of tetra-n-propylammonium per-ruthenate (VII) (6 mg). The reaction was stirred for 30 minutes and poured onto a silica bond elute (5 g) and eluted with ethylacetate to give 3-methyl-3-(4-(2-methylquinolin-4-ylmethoxy)phenyl)-1-(2-oxo-2-phenylethyl)pyrrolidin-2-one (90 mg). To a stirred solution of the above product in ethanol (2 ml) and water (2 ml) was added ammonium carbonate (110 mg) and potassium cyanide (25 mg). The mixture was worked up to give 5-(3-methyl-3-(4-(2-methylquinolin-4-ylmethoxy)phenyl)-2-oxopyrrolidin-1-ylmethyl)-5-phenylimidazolidine-2,4-dione (5 mg).

DEFINITIONS - Preferred Definitions:

B1 = (hetero)aryl or heterocyclyl (all optionally substituted by nitro, CF<sub>3</sub>, OCF<sub>3</sub>, halo, 1-4C alkyl (optionally substituted by one or more halo), 2-4C alkynyl, heteroaryl, OR<sub>9</sub>, CN, NR<sub>9</sub>R<sub>10</sub>, CONR<sub>9</sub>R<sub>10</sub> and/or NR<sub>9</sub>COR<sub>10</sub> (preferably phenyl, naphthyl, pyridyl, quinolinyl, isoquinolinyl, thienopyridyl, 1,6-naphthyridinyl, 2,3-methylenedioxypyrenyl, 3,4-methylenedioxypyrenyl, 1,6-naphthyridinyl, thienopyrimidinyl, pyridoimidazolyl, benzimidazolyl, benzofuranyl, benzothienyl, indolyl, benzothiazolyl, benzotriazolyl, benzisoxazolyl, benzisothiazolyl, indazolyl, indolizinyl, isobenzofuranyl, quinazolinyl, imidazopyridinyl, pyrazolopyridinyl, indolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl or isoindolinyl (each optionally substituted by nitro, CF<sub>3</sub>, OCF<sub>3</sub>, halo, 1-4C alkyl (optionally substituted by one or more fluoro), 2-4C alkynyl, heteroaryl, OR<sub>9</sub>, CN, NR<sub>9</sub>R<sub>10</sub>, CONR<sub>9</sub>R<sub>10</sub> and/or NR<sub>9</sub>COR<sub>10</sub> or 2-methylquinolin-4-yl or 2,5-dimethylphenyl); or

B1 = 2-4C alkenyl or 2-4C alkynyl optionally substituted by 1-4C alkyl, 3-6C cycloalkyl or heterocyclyl (preferably vinyl or ethynyl optionally substituted by 1-4C alkyl);

t = 1;

R7 = H, 1-4C alkyl, halo(1-4C alkyl), hydroxy(1-4C alkyl), 1-4C alkoxy(1-4C alkyl) or aryl; and

R14 = H, CH<sub>3</sub> or NH<sub>2</sub>.

L51 ANSWER 4 OF 85 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN  
 ACCESSION NUMBER: 2004-328245 [30] WPIX  
 DOC. NO. CPI: C2004-124409  
 TITLE: New hydantoin derivatives useful in the treatment of e.g. HIV infection, psoriasis, autoimmune diseases, tumor, gingivitis, and stroke.  
 DERWENT CLASS: B02 B03  
 INVENTOR(S): SHEPPECK, J  
 PATENT ASSIGNEE(S): (SHEP-I) SHEPPECK J; (BRIM) BRISTOL-MYERS SQUIBB CO  
 COUNTRY COUNT: 107  
 PATENT INFORMATION:

PATENT NO	KIND DATE	WEEK	LA	PG	MAIN IPC
-----------	-----------	------	----	----	----------

US 2004067996 A1 20040408 (200430)\* 43 A61K031-4166  
 WO 2004033632 A2 20040422 (200430) EN C12N000-00  
 RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS  
 LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW  
 W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK  
 DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP  
 KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG  
 PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ  
 VC VN YU ZA ZM ZW  
 AU 2003282920 A1 20040504 (200465) A61K031-4166  
 EP 1546109 A2 20050629 (200543) EN C07D215-20  
 R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LT LU LV  
 MC MK NL PT RO SE SI SK TR

## APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 2004067996	A1 Provisional	US 2002-416349P US 2003-677988	20021004 20031002
WO 2004033632	A2	WO 2003-US31347	20031002
AU 2003282920	A1	AU 2003-282920	20031002
EP 1546109	A2	EP 2003-774537 WO 2003-US31347	20031002 20031002

## FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2003282920	A1 Based on	WO 2004033632
EP 1546109	A2 Based on	WO 2004033632

PRIORITY APPLN. INFO: US 2002-416349P 20021004; US  
 2003-677988 20031002

## INT. PATENT CLASSIF.:

MAIN: A61K031-4166; C07D215-20; C12N000-00

SECONDARY: A61K031-4439; A61K031-4709; C07D233-72; C07D401-12

## BASIC ABSTRACT:

US2004067996 A UPAB: 20040511

NOVELTY - **Hydantoin** derivatives (I), their salts and prodrugs are new.

DETAILED DESCRIPTION - **Hydantoin** derivatives of formula (I), their salts and prodrugs are new.

E1 = CRARa1;

R1 = e.g. Q, 1-6C alkylene-Q, 2-6C alkenylene-Q, 2-6C alkynylene-Q or (E1)tO(E1)s-Q;

L = e.g. bond or CO;

Q = e.g. 3-13C carbocycle, or 5 - 14 membered heterocycle (containing 1 - 4 N, S, or S(O)p) (both optionally substituted), H, or CF3;

Z'a = 5 - 6-membered (hetero)aryl (optionally containing 1 - 3 heteroatoms) or (hetero)aryl (optionally fused to 5 - 6 membered carbocycle or heterocycle optionally containing 1 - 2 heteroatoms, and 1 - 2 double bonds) (both optionally substituted);

R11 = W'-U'-X-Y'-Z-Ua-Xa-Ya-Za;

W' = (E1)m, 2-3C alkenylene or 2-3C alkynylene;

U' = e.g. O, C(O), C(O)O, OC(O), or S(O)p;

X = absent, 1-3C alkylene, 2-3C alkenylene or 2-3C alkynylene;

Y', Ya = absent, O, S(O)p or C(O);

Z = 3-13C carbocycle or 5 - 14 membered heterocycle (containing 1 - 4 N, O or S(O)p) (both optionally substituted);

Ua = e.g. absent, O, C(O), C(O)O, OC(O), S(O)p, or NRa1S(O)2NRa1;  
Xa = e.g. absent, 1-10C alkylene, or 2-10C alkynylene;  
Za = 3-13C carbocycle or 5 - 14 membered heterocycle (containing 1 -  
4 N, O or S(O)p) (both optionally substituted);  
Ra1 = e.g. 2-6C alkenyl, 1-6C alkyl, or 2-6C alkynyl (all optionally  
monosubstituted), or H;  
R4, R5 = H, 1-4C alkyl, 2-4C alkenyl, or 2-4C alkynyl;  
m = 0 - 3;  
p = 0 - 2;  
r, s = 0 - 4; and  
t = 1 - 4.

Full Definitions are given in the DEFINITIONS (Full Definitions)  
section.

INDEPENDENT CLAIMS are included for the following:

(a) treatment of inflammatory disorders involving administration of  
(I) or its salt, in combination with at least one additional  
anti-inflammatory agents selected from selective COX-2 inhibitors,  
interleukin-1 antagonists, dihydroorotate synthase  
inhibitors, p38 MAP kinase inhibitors, tumor  
necrosis factor(TNF)- alpha inhibitors and  
TNF- alpha antibody or protein sequestration agents; and

(b) an article of manufacture comprising: a container (c1) containing  
a pharmaceutical composition (c2), and a package insert (c3) stating use  
of (c2) optionally in combination with a second therapeutic agent for the  
treatment of an inflammatory disorder. (c2) Comprises (I) or its salt.

ACTIVITY - Antiinflammatory; Antimicrobial; Ophthalmological;  
Hepatotropic; Antiallergic; Antiasthmatic; Anabolic; Eating-Disorders-Gen.;  
Antiarteriosclerotic; Dermatological; Immunosuppressive; Vasotropic;  
Immunomodulator; Cardiovascular-Gen.; Muscular-Gen.;  
Respiratory-Gen.; Anticoagulant; Antiulcer; Antipyretic; Antigout;  
Hemostatic; Anti-HIV; Antiarthritic; Antibacterial; Neuroprotective;  
Osteopathic; Antipsoriatic, Uropathic; Antirheumatic; Cytostatic;  
Cerebroprotective; Gastrointestinal-Gen.; Antiulcer.

MECHANISM OF ACTION - Matrix metalloproteinase-12  
(MMP-12) inhibitor; Tumor necrosis  
factor- alpha converting enzyme (TACE)  
inhibitor; Aggrecanase inhibitor. Test details are  
described, but no results for specific compounds given. In general, (I)  
showed Ki value of at most 10 mu M.

USE - For treatment of inflammatory disorder, a condition or disease  
mediated by MMPs, TACE, aggrecanase (including acute infection, acute  
phase response, age related macular degeneration, alcoholic liver disease,  
allergy, allergic asthma, anorexia, aneurysm, aortic aneurysm, asthma,  
atherosclerosis, atopic dermatitis, autoimmune disease, autoimmune  
hepatitis, Behcet's disease, cachexia, calcium pyrophosphate dihydrate  
deposition disease, cardiovascular effects, chronic fatigue syndrome,  
chronic obstruction pulmonary disease, coagulation, congestive heart  
failure, corneal ulceration, Crohn's disease, enteropathic arthropathy,  
Felty's syndrome, fever, fibromyalgia syndrome, fibrotic disease,  
gingivitis, glucocorticoid withdrawal syndrome, gout, graft versus host  
disease, hemorrhage, HIV infection, hyperoxic alveolar injury, infectious  
arthritis, inflammation, intermittent hydrarthrosis, Lyme disease,  
meningitis, multiple sclerosis, myasthenia gravis, mycobacterial  
infection, neovascular glaucoma, osteoarthritis, pelvic inflammatory  
disease, periodontitis, polymyositis/dermatomyositis, post-ischemic  
reperfusion injury, post-radiation asthenia, psoriasis, psoriatic  
arthritis, pulmonary emphysema, pyoderma gangrenosum, relapsing  
polychondritis, Reiter's syndrome, rheumatic fever, rheumatoid arthritis,  
sarcoidosis, scleroderma, sepsis syndrome, Still's disease, shock,  
Sjogren's syndrome, skin inflammatory diseases, solid tumor growth and

tumor invasion by secondary metastases, spondylitis, stroke, systemic lupus erythematosus, ulcerative colitis, uveitis, vasculitis, and Wegener's granulomatosis (claimed).

**ADVANTAGE** - The compounds exhibit selectivity for MMP and TACE, hence are potent MMP-12 inhibitors; eliminate undesirable tissue destruction found in variety of human diseases; can be manufactured economically; and provide effective treatment for wide variety of diseases e.g. respiratory diseases and metastatic diseases.

Dwg.0/0

FILE SEGMENT: CPI

FIELD AVAILABILITY: AB; GI; DCN

MANUAL CODES: CPI: B06-D02; B06-F01; B06-H; B07-D09; B14-A01;  
B14-A02B1; B14-C01; B14-C02; B14-C03; B14-C04;  
B14-C06; B14-C09; B14-D03; B14-D05C; B14-D06;  
B14-D07C; B14-E08; B14-E10C; B14-E11; B14-F01;  
B14-F02; B14-F04; B14-F05; B14-F07; B14-F08;  
B14-G02; B14-H01; B14-J05; B14-K01; B14-K01A;  
B14-L06; B14-L07; B14-N01; B14-N03; B14-N06B;  
B14-N07; B14-N12; B14-N16; B14-N17; B14-S01;  
B14-S05; B14-S06

TECH UPTX: 20040511

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: The hydantoin heterocycles are synthesized by methods as described in Matthews J, and Rivero R. A, J. Org. Chem. 1997, 62, 6090 - 6092.

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Article: The article additionally comprises another container containing (c1) and (c2); and (c3) is located within or outside of the another container.

ABEX UPTX: 20040511

SPECIFIC COMPOUNDS - 14 Compounds are specifically claimed as (I), e.g. N-(2-(2,5-dioxoimidazolidin-4-yl)phenyl)-4-((2-methylquinolin-4-yl)methoxy)benzamide trifluoroacetate.

ADMINISTRATION - Dosage is 0.001 - 1000 (preferably 0.01 - 100, especially 1 - 20) mg/kg for oral administration; and is 1 - 10 mg/kg/minute for intravenous administration during constant rate infusion. Administration is also by topical (e.g. transdermal), intranasal or parenteral route.

EXAMPLE - To a solution of 2-aminobenzyl alcohol (0.5 g) in dichloromethane (DCM)/10% NaHCO<sub>3</sub> (1:1, 50 ml) was added 4-((2-methyl-4-quinolinyl)methoxy)benzoyl chloride (1.5 g). After stirring for 24 hours, the reaction mixture was filtered, and the resultant residue was washed and dried to give 2-(4-((2-methyl-4-quinolinyl)methoxy)benzoylamino)benzyl alcohol (Ia). A reaction mixture of (Ia) (398 mg) in DCM/dimethyl formamide (DMF) (1:1, 50 ml) and Dess-Martin periodinane (1 g) was stirred for 18 hours, and then extracted from 1N NaOH with EtOAc. After work up, 2-(4-((2-methyl-4-quinolinyl)methoxy)benzoylamino)benzaldehyde (Ib) was obtained. A solution of (Ib) (396 mg) in ethanol/water (1:1, 50 ml) was treated with ammonium carbonate (960 mg) and potassium cyanide (130 mg) at 80 degrees C for 24 hours; and worked up to give N-(2-(2,5-dioxoimidazolidin-4-yl)phenyl)-4-((2-methylquinolin-4-yl)methoxy)benzamide trifluoroacetate (47 mg).

DEFINITIONS - Full Definitions:

E1 = CRaRa1;

R1 = Q, 1-6C alkylene-Q, 2-6C alkenylene-Q, 2-6C alkenylene-Q,  
(E1)tO(E1)s-Q, (E1)tNRa(E1)s-Q, (E1)rC(O)(E1)s-Q, -(E1)rC(O)O(E1)s-Q,  
(E1)tOC(O)(E1)s-Q, -(E1)rC(O)NRaRa1, (E1)rC(O)NRa(E1)-Q,  
(E1)tNRaC(O)(E1)-Q, (E1)tOC(O)O(E1)s-Q, (E1)tOC(O)NRa(E1)s-Q,  
(E1)tNRaC(O)O(E1)s-Q, (E1)tNRaC(O)NRa(E1)s-Q, (E1)tS(E1)s-Q,  
(E1)tS(O)(E1)s-Q, (E1)rS(O)2(E1)s-Q, (E1)S(O)2NRa(E1)s-Q,  
(E1)tNRaSO2(E1)s-Q or (E1)tNRaSO2NRa(E1)s-Q;

L = bond, CO, CR<sub>2</sub>R<sub>3</sub>;

R<sub>2</sub> = Q<sub>1</sub>, 1-6C alkylene-Q<sub>1</sub>, 2-6C alkenylene-Q<sub>1</sub>, 2-6C alkenylene-Q<sub>1</sub>, (E1)rO(E1)s-Q<sub>1</sub>, (E1)rNRa(E1)s-Q<sub>1</sub>, (E1)rC(O)(E1)s-Q<sub>1</sub>, (E1)rC(O)O(E1)s-Q<sub>1</sub>, (E1)rOC(O)(E1)s-Q<sub>1</sub>, (E1)rC(O)NRaRa1, (E1)rC(O)NRa(E1)s-Q<sub>1</sub>, (E1)rNRaC(O)(E1)s-Q<sub>1</sub>, (E1)rOC(O)O(E1)s-Q<sub>1</sub>, (E1)rOC(O)NRa(E1)s-Q<sub>1</sub>, (E1)rNRaC(O)NRa(E1)s-Q<sub>1</sub>, (E1)2rS(O)p(E1)s-Q<sub>1</sub>, (E1)rSO2NRa(E1)s-Q<sub>1</sub>, (E1)rNRaSO2(E1)s-Q<sub>1</sub> or (E1)rNRaSO2NRa(E1)s-Q<sub>1</sub>;

R<sub>3</sub> = Q, 1-6C alkylene-Q, 2-6C alkenylene-Q, 2-6C alkenylene-Q, (E1)rO(E1)s-Q, (E1)rNRa(E1)s-Q, (E1)rC(O)(E1)s-Q, -(E1)rC(O)O(E1)s-Q, (E1)rC(O)NRaRa1, (E1)rC(O)NRa(E1)s-Q, (E1)rNRaC(O)(E1)s-Q, (E1)rS(O)p(E1)s-Q, (E1)rS(O)2NRa(E1)s-Q or (E1)rNRaSO2(E1)s-Q;

Q = 3-13C carbocycle, or 5 - 14 membered heterocycle (containing 1 - 4 N, S, or S(O)p) (both optionally substituted with 1 - 4 R<sub>d</sub>), H, CHF<sub>2</sub>, CH<sub>2</sub>F or CF<sub>3</sub>;

Q<sub>1</sub> = 3-13C carbocycle or 5 - 14 membered heterocycle (containing 1 - 4 N, NR<sub>7</sub>, O or S(O)p) (both optionally substituted with 1 - 4 R<sub>d</sub>) or H;

Z'a = 5 - 6-membered (hetero)aryl (optionally containing 1 - 3 N, NR<sub>7</sub>, O or S(O)p) or (hetero)aryl (optionally fused to 5 - 6 membered carbocycle or heterocycle optionally containing 1 - 2 N, NR<sub>7</sub>, O or S(O)p, and 0 - 2 double bonds) (both optionally substituted by 1 - 3 R<sub>6</sub>);

R<sub>11</sub> = W'-U'-X-Y'-Z-Ua-Xa-Ya-Za;

W' = (E1)m, 2-3C alkenylene or 2-3C alkynylene;

U' = O, NRa1, C(O), CRa(OH), C(O)O, OC(O), C(O)NRa1, NRa1C(O), OC(O)O, OC(O)NRa1, NRa1C(O)O, NRa1C(O)NRa1, S(O)p, S(O)pNRa1, NRa1S(O)p or NRa1SO2NRa1;

X = absent, 1-3C alkylene, 2-3C alkenylene or 2-3C alkynylene;

Y, Ya = absent, O, NRa1, S(O)p or C(O);

Z = 3-13C carbocycle or 5 - 14 membered heterocycle (containing 1 - 4 N, O or S(O)p) (both optionally substituted with 1 - 5 R<sub>b</sub>);

Ua = absent, O, NRa1, C(O), CRa(OH), C(O)O, OC(O), C(O)NRa1, NRa1C(O), OC(O)O, OC(O)NRa1, NRa1C(O)O, NRa1C(O)NRa1, S(O)p, S(O)pNRa1, NRa1S(O)p or NRa1S(O)2NRa1;

Xa = absent, 1-10C alkylene, 2-10C alkenylene or 2-10C alkynylene;

Za = 3-13C carbocycle or 5 - 14 membered heterocycle (containing 1 - 4 N, O or S(O)p) (both optionally substituted with 1 - 5 R<sub>c</sub>);

Ra = H, 1-6C alkyl, phenyl, or benzyl;

Ra1, Ra3 = 2-6C alkenyl, 1-6C alkyl or 2-6C alkynyl (all optionally monosubstituted with R<sub>c1</sub>), (CH<sub>2</sub>)r-(3 - 8-membered carbocyclic or heterocyclic ring optionally containing 1 - 2 N, NRa2, O, and S(O)p) (optionally substituted with 1 - 3 R<sub>c1</sub>) or H;

NRaRa1 = 5 or 6 membered heterocycle (optionally containing 1 additional N, NRa2, O, or S(O)p);

Ra2 = 1-4C alkyl, phenyl, or benzyl;

Rb = 1-6C alkyl (optionally monosubstituted with R<sub>c1</sub>, -SRa, T1, CHF<sub>2</sub>, CH<sub>2</sub>F, or phenyl;

T1 = -ORa, halo, =O, CN, NO<sub>2</sub>, -NRaRa1, -C(O)Ra, -C(O)ORa, -C(O)NRaRa1, -C(S)NRaRa1, -NRaC(O)NRaRa1, -OC(O)NRaRa1, -NRaC(O)ORA, S(O)2NRaRa1, -NRaS(O)2Ra3, -NRaS(O)2NRaRa1, -OS(O)2NRaRa1, -S(O)pRa3, CF<sub>3</sub> or -CF<sub>2</sub>CF<sub>3</sub>;

Rc = 1-6C alkyl, 2-6C alkenyl, (E1)r-3-10C carbocycle, or (E1)r-5 - 14-membered heterocycle (containing 1 - 4 N, O, and S(O)p) (all optionally mono- or di-substituted with R<sub>c1</sub>), H, halo, =O, CN, NO<sub>2</sub>, CF<sub>3</sub>, -CF<sub>2</sub>CF<sub>3</sub>, CH<sub>2</sub>F, CHF<sub>2</sub>, -(E1)rORa, -(E1)rNRaRa1, -(E1)rC(=NCN)NRaRa1,

-(E1)rC(=NRa)NRaRa1, -(E1)rC(=NORa)NRaRa1, -(E1)rC(O)NRaOH, -(E1)rC(O)Ra1, (E1)rC(O)ORA1, -(E1)rC(S)ORA1, -(E1)rC(O)NRaRa1, -(E1)rNRaC(O)Ra1, -(E1)rC(S)NRaRa1, -(E1)rOC(O)NRaRa1, -(E1)rNRaC(O)ORA1, (E1)rNRaC(O)NRaRa1, -(E1)rS(O)pRa3, (E1)rSO2NRaRa1, (E1)rNRaSO2Ra3, or (E1)rNRaSO2NRaRa1;

CR<sub>c</sub>Rc = 3 - 8 membered carbocyclic or heterocyclic spiro ring (optionally containing 1 - 4 O, N, and S(O)p, and 1 - 2 double bonds; and optionally mono- or di-substituted with R<sub>c1</sub>);

$\text{CRC}+\text{CRC}$  = 5 - 7 membered carbocyclic or heterocyclic ring D (optionally containing 1 - 2 O, N, and S(O)p, and 1 - 3 double bonds; and optionally mono- or di-substituted with  $\text{Rc1}$ );  
 $\text{Rc1}$  = H, 1-4C alkyl, -ORa, halo, =O, CF<sub>3</sub>, CN, NO<sub>2</sub>, -C(O)Ra, -C(O)ORA,  
-C(O)NRaRa, or -S(O)pRa;  
 $\text{Rd}$  = 1-6C alkyl, T<sub>1</sub>, 3-10C carbocycle, or 5 - 14 membered heterocycle (containing 1 - 4 N, O, and S(O)p);  
 $\text{Re}$  = 3-10C carbocycle or 5 - 10 membered heterocycle containing 1 - 4 N, O, and S(O)p (both optionally mono- or di-substituted with  $\text{Rc1}$ ), H, 1-6C alkyl, 1-6C alkoxy, phenoxy or benzoxy;  
 $\text{R4}$ ,  $\text{R5}$  = H, 1-4C alkyl, 2-4C alkenyl, or 2-4C alkynyl;  
 $\text{R6}$  = T<sub>2</sub>, H, halo, =O, CN, NO<sub>2</sub>, CF<sub>3</sub>, -CF<sub>2</sub>CF<sub>3</sub>, (E1)rORA, -(E1)rNRaRa<sub>1</sub>, (E1)rC(O)NRaOH, (E1)rC(O)Ra, -(E1)rC(O)-(E1)sRe, (E1)rC(O)ORA<sub>1</sub>, (E1)rC(S)ORA<sub>1</sub>, -(E1)rC(O)NRaRa<sub>1</sub>, (E1)rNRaC(O)Ra<sub>1</sub>, (E1)rC(S)NRaRa<sub>1</sub>, -(E1)rOC(O)NRaRa<sub>1</sub>, (E1)rNRaC(O)ORA<sub>1</sub>, (E1)rNRaC(O)NRaRa<sub>1</sub>, (E1)rS(O)pRa<sub>3</sub>, -(E1)rSO<sub>2</sub>NRaRa<sub>1</sub>, (E1)rNRaSO<sub>2</sub>Ra<sub>3</sub>, or (E1)rNRaSO<sub>2</sub>NRaRa<sub>1</sub>;  
 $\text{T2}$  = 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl, (E1)r-3-10C carbocycle or (E1)r-5 - 10-membered heterocycle (containing 1 - 4 N, O, and S(O)p) (all optionally mono- or di-substituted with  $\text{Rc1}$ );  
 $\text{R7}$  = H, (E1)tNRaRa<sub>1</sub>, (E1)rC(O)NRaOH, -(E1)rC(O)(E1)sRe, (E1)rC(O)ORA<sub>1</sub>, (E1)rC(S)ORA<sub>1</sub>, (E1)rC(O)NRaRa<sub>1</sub>, (E1)tNRaC(O)Ra<sub>1</sub>, (E1)rC(S)NRaRa<sub>1</sub>, (E1)tOC(O)NRaRa<sub>1</sub>, (E1)tNRaC(O)ORA<sub>1</sub>, (E1)tNRaC(O)NRaRa<sub>1</sub>, (E1)rS(O)pRa<sub>3</sub>, -(E1)rSO<sub>2</sub>NRaRa<sub>1</sub>, (E1)tNRaSO<sub>2</sub>Ra<sub>3</sub>, (E1)tNRaSO<sub>2</sub>NRaRa<sub>1</sub> or  $\text{T2}$ ;  
 $m$  = 0 - 3;  
 $p$  = 0 - 2;  
 $r$ ,  $s$  = 0 - 4; and  
 $t$  = 1 - 4.  
Provided that:  
(1) when L is a bond, CHR<sub>2</sub> or CHR<sub>3</sub>, and Z is phenyl, then Za is other than phenyl;  
(2) when L is a bond or CH<sub>2</sub>, and Z is phenyl or naphthyl, then Za is other than a 5 or 6-membered heteroaryl or a **hydantoin** moiety;  
(3) when L is a bond, Z is phenyl, -Ua-Xa-Ya- forms 1-2C alkylene, and Za is benzimidazolyl, then Rc is other than C(O)ORA<sub>1</sub>;  
(4) when Z is benzo(1,4)oxazinyl, pyrrolidinyl, piperidinyl or azepanyl, then -Ua-Xa-Ya- forms other than a bond or 1-4C alkylene;  
(5) when Z is 2H-benzopyranone, then Za is other than a galactopyranosyloxy moiety;  
(6) when L is a bond, Z is other than thiadiazinyl; and  
(7) when CRCRC forms 3 - 8 membered ring, then the ring contains other than S-S, O-O, or S-O bond; and  
(8) combination of U, Y, Z, Ua, Ya, and Za is other than N-N, N-O, O-N, O-O, S(O)p-O, O-S(O)p, S(O)p-S(O)p group.

L51 ANSWER 5 OF 85 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN  
ACCESSION NUMBER: 2003-289959 [28] WPIX  
DOC. NO. CPI: C2003-075289  
TITLE: New bicyclic **hydroxamate** derivatives are  
inhibitors of matrix  
**metalloproteinases** and/or **TNF-**  
**alpha** converting enzyme, useful for  
treating e.g. inflammatory disorders.  
DERWENT CLASS: B02  
INVENTOR(S): DUAN, J; SHEPPECK, J E; SHEPPECK, J  
PATENT ASSIGNEE(S): (BRIM) BRISTOL-MYERS SQUIBB CO PATENT DEPT; (DUAN-I) DUAN  
J; (SHEP-I) SHEPPECK J E; (BRIM) BRISTOL-MYERS SQUIBB  
PHARMA CO; (BRIM) BRISTOL-MYERS SQUIBB CO  
COUNTRY COUNT: 101  
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
WO 2003016248	A2	20030227 (200328)*	EN	102	C07C000-00	
RW:	AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SK SL SZ TR TZ UG ZM ZW					
W:	AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG UZ VC VN YU ZA ZM ZW					
US 2003130257	A1	20030710 (200347)			A61K031-553	
US 6770647	B2	20040803 (200451)			C07D471-04	
AU 2002324716	A1	20030303 (200452)			C07C000-00	

## APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2003016248	A2	WO 2002-US26018	20020815
US 2003130257	A1 Provisional	US 2001-313052P	20010817
		US 2002-219426	20020815
US 6770647	B2 Provisional	US 2001-313052P	20010817
		US 2002-219426	20020815
AU 2002324716	A1	AU 2002-324716	20020815

## FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2002324716	A1 Based on	WO 2003016248

PRIORITY APPLN. INFO: US 2001-313052P 20010817; US  
2002-219426 20020815

## INT. PATENT CLASSIF.:

MAIN: A61K031-553; C07C000-00; C07D471-04  
SECONDARY: A61K031-4985; A61K031-519; A61K031-538; A61K031-542;  
A61K031-55; A61K031-5513; A61P009-10; A61P037-08;  
C07D487-04

## BASIC ABSTRACT:

WO2003016248 A UPAB: 20031125

NOVELTY - Bicyclic hydroxamate derivatives (I) are new.

DETAILED DESCRIPTION - Bicyclic hydroxamate derivatives of formula (I), and their salts, are new.

A = -C(O)NHOH, -C(O)NHOR5, -C(O)NHOR6, -N(OH)COR5, N(OH)CHO or -CH2SH;

B = a 5-7 membered heterocyclic ring including B1 and B2, optionally substituted with R2;

B1, B2 = 0-3C and 0-1 heteroatoms (O, N or S(O)p), optionally substituted with carbonyl;

C = a 5-10 membered aromatic ring comprising 1-9C and 0-4 heteroatoms (O, N or S(O)p); optionally substituted with R3 and R4;

R1 = U-X-Y-Z-Ua-Xa-Ya-Za;

U = C(O), C(O)O, C(O)NR1a, S(O)p or S(O)pNR1a;

X = absent or 1-10C alkylene, 2-10C alkenylene or 2-10C alkynylene;

Y = absent or O, NR1a, S(O)p or C(O);

Z = 3-13C carbocycle substituted with 0-5Rb; or 5-14 membered heterocycle comprising C and 1-4 heteroatoms (N, O or S(O)p) substituted with 0-5 Rb;

Ua = e.g. absent or O, NR1a, C(O), C(O)O, OC(O);

Xa = absent or 1-4C alkylene, 2-4C alkenylene or 2-4C alkynylene;

$\text{Y}_\alpha$  = absent or O, NR1a, S(O)p or C(O);  
 $\text{Z}_\alpha$  = a 3-13C carbocycle substituted with 0-5 R<sub>c</sub>; or a 5-14 membered heterocycle comprising C and 1-4 heteroatoms (N, O or S(O)p) substituted with 0-5 R<sub>c</sub>;  
R<sub>2</sub> = H; or 1-6C alkyl, 2-6C alkenyl or 2-6C alkynyl, each substituted with 0-1 R<sub>b</sub>;  
R<sub>3</sub> = e.g. R<sub>2</sub>; 3-10C carbocycle or -(CH<sub>2</sub>)<sub>r</sub>-(3-10C carbocycle);  
R<sub>4</sub> = e.g. R<sub>2</sub>, OR<sub>a</sub>, Cl, F, Br, I, =O, CN;  
R<sub>a</sub> = H or 1-6C alkyl;  
R<sub>1a</sub> = e.g. H; 1-6C alkyl, 2-6C alkenyl or 2-6C alkynyl;  
R<sub>b</sub> = R<sub>4</sub>, CHF<sub>2</sub>, CH<sub>2</sub>F or phenyl;  
R<sub>c</sub> = e.g. H; 1-6C alkyl, 2-6C alkenyl or 2-6C alkynyl;  
R<sub>5</sub> = 1-10C alkyl substituted with 0-2 R<sub>b</sub>; or 1-8C alkyl substituted with 0-2 R<sub>e</sub>;  
R<sub>e</sub> = phenyl or biphenyl, each substituted with 0-2 R<sub>b</sub>;  
R<sub>6</sub> = e.g. phenyl, naphthyl, 1-10C alkyl-phenyl-(1-6C)alkyl-;  
n, r = 0-4;  
p = 0-2;  
provided that:  
(i) ring B contains other than an N-S, N-O or N-N bond;  
(ii) Ua-Xa-Ya forms a spacer of 2 or more atoms, other than CH=CH- or -C triple bond C-;  
(iii) U, Y, Z, Ua, Ya and Za do not combine to form N-N, N-O, O-N, O-O, S(O)p-O, O-S(O)p or S(O)p-S(O)p;  
(iv) when rings B and C form tetrahydroisoquinoline, and A is C(O)NHOH, then R<sub>1</sub> is other than (4-((2-methyl-4-quinolinyl)methoxy)phenyl)acetyl, ((2-hydroxybenzoyl)amino)benzenesulfonyl, ((4-fluorophenyl)methoxy)benzenesulfonyl or ((4-methoxyphenyl)carbamate)benzenesulfonyl;  
(v) when rings B and C form tetrahydro-furo(2,3-c)pyridine, A is C(O)NHOH, and U is SO<sub>2</sub>, then Z is other than phenyl;  
(vi) when rings B and C form tetrahydro-1H-(1,4)-benzodiazepine, A is -C(O)NHOH, U is SO<sub>2</sub>, then Z is other than phenyl;  
(vii) when U is SO<sub>2</sub>, then Ua-Xa-Ya is other than -OCH<sub>2</sub>-C triple bond C-, -NHCH<sub>2</sub>-C triple bond C-, -CH<sub>2</sub>CH<sub>2</sub>-C triple bond C- or -SCH<sub>2</sub>-C triple bond C-;  
(viii) when U is SO<sub>2</sub> and Z is phenyl, then Ua is other than OC(O).  
Full definitions are given in the DEFINITIONS (Full Definitions) field.

ACTIVITY - Antiallergic; antiasthmatic; antiarteriosclerotic; dermatological; antiinflammatory; hepatotropic; virucide; vasotropic; immunomodulator; ophthalmological; antipyretic; antigout; immunosuppressive; hemostatic; anti-HIV; antiarthritic; antibacterial; osteopathic; vasotropic; uropathic; antirheumatic; cytostatic; cerebroprotective.

MECHANISM OF ACTION - Matrix metalloproteinases inhibitors; TNF-alpha converting enzyme inhibitors; aggrecanase inhibitors.

In tests to determine MMP inhibitory activity, test compounds (I) had Ki values at most 10  $\mu\text{M}$ .

USE - For treating conditions or diseases mediated by matrix metalloproteinases (MMPs), TNF-alpha converting enzyme (TACE) and/or aggrecanase; particularly acute infection, acute phase response, age related macular degeneration, alcoholic liver disease, allergy, allergic asthma, anorexia, aneurism, aortic aneurism, asthma, atherosclerosis, atopic dermatitis, autoimmune disease, autoimmune hepatitis, Behcet's syndrome, cachexia, calcium pyrophosphate dihydrate deposition disease, cardiovascular effects, chronic fatigue syndrome, chronic obstruction pulmonary disease, coagulation, congestive heart failure, corneal ulceration, Crohn's disease, enteropathic arthropathy, Felty's syndrome, fever, fibromyalgia syndrome, fibrotic disease, gingivitis, glucocorticoid

withdrawal syndrome, gout, graft versus host disease, hemorrhage, HIV infection, hyperoxic alveolar injury, infectious arthritis, inflammation, intermittent hydrarthrosis, Lyme disease, meningitis, multiple sclerosis, myasthenia gravis, mycobacterial infection, neovascular glaucoma, osteoarthritis, pelvic inflammatory disease, periodontitis, polymyositis/dermatomyositis, post ischemic reperfusion injury, psoriatic arthritis, pulmonary emphysema, pyoderma gangrenosum, relapsing polychondritis, Reiter's syndrome, rheumatic fever, rheumatoid arthritis, sarcoidosis, scleroderma, sepsis syndrome, Still's disease, shock, Sjogren's syndrome, skin inflammatory diseases, solid tumor growth and tumor invasion by secondary metastases, spondylitis, stroke, systemic lupus erythematosus, ulcerative colitis, uveitis, vasculitis or Wegener's granulomatosis (claimed).

Inflammatory disorders can be treated by administration of (I) in combination with 1 or more antiinflammatory agents selected from selective COX-2 inhibitors, interleukin-1 antagonists, dihydroorotate synthase inhibitors, p38 MAP kinase inhibitors, TNF- alpha inhibitors, THF- alpha sequestration agents, and methotrexate (claimed).

Dwg.0/0

FILE SEGMENT: CPI

FIELD AVAILABILITY: AB; GI; DCN

MANUAL CODES: CPI: B06-H; B14-A01; B14-A02B1; B14-B04A; B14-C02; B14-C03; B14-C04; B14-C09A; B14-C09B; B14-D07C; B14-E08; B14-E10C; B14-E11; B14-F01; B14-F02; B14-F05; B14-F07; B14-F08; B14-G02A; B14-G02D; B14-H01; B14-J01; B14-K01; B14-K01A; B14-N03; B14-N06B; B14-N12; B14-N16; B14-N17; B14-N17C; B14-S01

TECH UPTX: 20031125

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: (I) can be prepared e.g. by treating a methyl ester of formula (II) with hydroxylamine under basic conditions to give a compound of formula (IA).

ABEX UPTX: 20031125

SPECIFIC COMPOUNDS - 10 Compounds (I) are specifically claimed, e.g. N-hydroxy-6-((4-((2-methyl-4 quinolinyl)methoxy)phenyl)acetyl)-5,6,7,8-tetrahydro-1,6 naphthyridine-7-carboxamide; and N-hydroxy-5-((4-(2-methyl-4 quinolinyl)methoxy)phenyl)sulfonyl)-4,5,6,7 tetrahydro(1,3)thiazolo(4,5-c)pyridine-6-carboxamide.

ADMINISTRATION - Administration is by conventional routes. Daily oral dosage is 0.001-1000 (preferably 1-20) mg/kg. Intravenous dosage is 1-10mg/kg/minute during constant rate infusion.

EXAMPLE - Diethyl 6-acetyl-5,8-dihydropyrido(3,4-b)pyrazine 7,7(6H)-dicarboxylate (0.557mmol) was dissolved in 6M HCl (3ml) and refluxed for 1.5 hours. The mixture was cooled, concentrated and taken up in saturated HCl in MeOH (10ml). After refluxing overnight, the mixture was concentrated to give the crude amino ester HCl salt. This was taken up in MeOH (10ml) and hydrogen chloride was bubbled through the solution for 30 minutes. The mixture was stirred overnight, then concentrated, dried, and dissolved in DMF (2ml).

(4-((2-Methyl-4 quinolinyl)methoxy)phenyl)acetic acid (205mg), diisopropylethylamine (486microl) and PyBOP (377mg) were added. After stirring overnight, the mixture was partitioned between EtOAc and saturated NaHCO<sub>3</sub> and separated. The organic phase was dried, filtered, concentrated and passed through a silica plug. Purification of the residue by HPLC gave methyl 6-((4-((2-methyl-4 quinolinyl)methoxy)phenyl)acetyl)-5,6,7,8-tetrahydropyrido(3,4 b)pyrazine-7-carboxylate.

An anhydrous solution of hydroxylamine in MeOH (1.5ml, 1.64M) was added to the bis-TFA salt of this compound (62mg). After 30 minutes, the mixture was concentrated and purified by HPLC to give N-hydroxy-6-((4-((2-

methyl-4-quinolinyl)methoxy)phenyl)acetyl)-5,6,7,8 tetrahydropyrido(3,4-b)pyrazine-7-carboxamide (25mg, 37%) as the TFA salt after lyophilization.

**DEFINITIONS - Full Definitions:**

A = -C(O)NHOH, -C(O)NHOR5, -C(O)NHOR6, -N(OH)COR5, N(OH)CHO or -CH2SH;

B = a 5-7 membered heterocyclic ring including B1 and B2, optionally substituted with R2;

B1, B2 = 0-3C and 0-1 heteroatoms (O, N or S(O)p), optionally substituted with carbonyl;

C = a 5-10 membered aromatic ring comprising 1-9C and 0-4 heteroatoms (O, N or S(O)p); optionally substituted with R3 and R4;

R1 = U-X-Y-Z-Ua-Xa-Ya-Za;

U = C(O), C(O)O, C(O)NR1a, S(O)p or S(O)pNR1a;

X = absent or 1-10C alkylene, 2-10C alkenylene or 2-10C alkynylene;

Y = absent or O, NR1a, S(O)p or C(O);

Z = 3-13C carbocycle substituted with 0-5Rb; or 5-14 membered heterocycle comprising C and 1-4 heteroatoms (N, O or S(O)p) substituted with 0-5 Rb;

Xa = absent or 1-4C alkylene, 2-4C alkenylene or 2-4C alkynylene;

Ya = absent or O, NR1a, S(O)p or C(O);

Za = a 3-13C carbocycle substituted with 0-5 Rc; or a 5-14 membered heterocycle comprising C and 1-4 heteroatoms (N, O or S(O)p) substituted with 0-5 Rc;

R2 = H; or 1-6C alkyl, 2-6C alkenyl or 2-6C alkynyl, each substituted with 0-1 Rb;

Ra = H or 1-6C alkyl;

Rb = R4, CHF2, CH2F or phenyl;

R5 = 1-10C alkyl substituted with 0-2 Rb; or 1-8C alkyl substituted with 0-2 Re;

Re = phenyl or biphenyl, each substituted with 0-2 Rb;

n, r = 0-4;

p = 0-2;

Ua = absent or O, NR1a, C(O), C(O)O, OC(O), C(O)NR1a, NR1aC(O), OC(O)O, OC(O)NR1a, NR1aC(O)O, NR1aC(O)NR1a, S(O)p, S(O)pNR1a, NR1aS(O)p or NR1aSO2NR1a;

R3 = R2; 3-10C carbocycle or -(CH2)r-(3-10C carbocycle), each substituted with 0-2 Rb; or -(CH2)r-(5-10)membered heterocycle comprising C and 1-4 heteroatoms (N, O or S(O)p) substituted with 0-2 Rb;

R4 = R2, ORa, Cl, F, Br, I, =O, CN, NO2, NRaR1a, C(O)Ra, C(O)ORA, C(O)NRaR1a, NRaC(O)Ra, C(S)NRaR1a, NRaC(O)NRaR1a, OC(O)NRaR1a, NRaC(O)ORA, S(O)2NRaR1a, NRaS(O)2Ra3, NRaS(O)2NRaR1a, OS(O)2NRaR1a, NRaS(O)2Ra3, S(O)pRa3, CF3, OCF3 or CF2CF3;

R1a, Ra3 = H; 1-6C alkyl, 2-6C alkenyl or 2-6C alkynyl, each substituted with 0-1 Rc1; or -(CH2)r-(3-8)membered carbocyclic or heterocyclic ring comprising C and 0-2 ring heteroatoms (N, NRa2, O or S(O)p) substituted with 0-3 Rc1; or Ra and R1a together with N to which they are attached may form a 5 or 6-membered heterocycle comprising C and 0-1 additional heteroatoms (N, NRa2, O or S(O)p);

Ra2 = 1-4C alkyl, phenyl or benzyl;

Rc = H; 1-6C alkyl, 2-6C alkenyl or 2-6C alkynyl, each substituted with 0-2 Rc1; ORa, Cl, F, Br, I, =O, CN, NO2, CF3, CF2CF3, CH2F, (CRaR1a)nNRaR1a, (CRaR1a)nC(=NCN)NRaR1a, (CRaR1a)nC(=NRa)NRaR1a,

(CRaR1a)nC(O)NRaOH, (CRaR1a)nC(O)R1a, (CRaR1a)nC(O)OR1a,

(CRaR1a)nC(S)OR1a, (CRaR1a)nC(O)NRaR1a, (CRaR1a)NRaC(O)R1a,

(CRaR1a)nC(S)NRaR1a, (CRaR1a)nOC(O)NRaR1a, (CRaR1a)nNRaC(O)OR1a,

(CRaR1a)nNRaC(O)NRaR1a, (CRaR1a)nS(O)pRa3, (CRaR1a)nSO2NRaR1a,

(CRaR1a)nNRaSO2Ra3, (CRaR1a)nNRaSO2NRaR1a; -C(RaR1a)n-(3-10C) carbocycle substituted with 0-2 Rc1; or -(CRaR1a)n-(5-14)membered heterocycle

comprising C and 1-4 heteroatoms (N, O or S(O)p) substituted with 0-2 Rc1;

Rc1 = H, 1-4C alkyl, ORa, Cl, F, Br, I, =O, CF3, CN, NO2, C(O)Ra, C(O)ORA, C(O)NRaRa or S(O)pRa; .

R6 = phenyl, naphthyl, 1-10C alkyl-phenyl-(1-6C)alkyl-, 3-11C cycloalkyl, 1-6C alkylcarbonyloxy-(1-3C)alkyl, 1-6C alkylcarbonyloxy-(1-3C)alkyl, 2-10C alkoxy carbonyl, 3-6C cycloalkylcarbonyloxy-(1-3C)alkyl, 3-6C cycloalkoxycarbonyloxy-(1-3C)alkyl, 3-6C cycloalkoxycarbonyl, phenoxy carbonyl, phenoxy carbonyloxy-(1-3C)alkyl, phenyl carbonyloxy-(1-3C)alkyl, 1-6C alkoxy-(1-6C)alkylcarbonyloxy-(1-3C)alkyl, (5-(1-5C alkyl)-1,3-dioxa-cyclopenten-2-one-yl)methyl, (5-(Ra)-1,3-dioxa-cyclopenten-2-one-yl)methyl, (5-aryl-1,3-dioxa-cyclopenten-2-one-yl)methyl, 1-10C alkyl-NR7R7a, -CH(R8)OC(=O)R9 or -CH(R8)OC(=O)OR9; R7, R7a = H, 1-10C alkyl, 2-6C alkenyl, 3-6C cycloalkyl-(1-3C)alkyl or phenyl-(1-6C)alkyl;

R8 = H or 1-4C linear alkyl;

R9 = H; 1-8C alkyl or 3-8C cycloalkyl, each substituted with 1-2 Rf; or phenyl substituted with 0-2 Rb;

Rf = 1-4C alkyl, 3-8C cycloalkyl, 1-5C alkoxy, or phenyl substituted with 0-2 Rb.

provided that:

- (i) ring B contains other than an N-S, N-O or N-N bond;
- (ii) Ua-Xa-Ya forms a spacer of 2 or more atoms, other than CH=CH- or -C<sub>triple</sub>bondC-;
- (iii) U, Y, Z, Ua, Ya and Za do not combine to form N-N, N-O, O-N, O-O, S(O)p-O, O-S(O)p or S(O)p-S(O)p;
- (iv) when rings B and C form tetrahydroisoquinoline, and A is C(O)NHOH, then R1 is other than (4-((2-methyl-4 quinolinyl)methoxy)phenyl)acetyl, ((2 hydroxybenzoyl)amino)benzenesulfonyl, ((4 fluorophenyl)methoxy)benzenesulfonyl or ((4 methoxyphenyl)carbamate)benzenesulfonyl;
- (v) when rings B and C form tetrahydro-furo(2,3-c)pyridine, A is C(O)NHOH, and U is SO<sub>2</sub>, then Z is other than phenyl;
- (vi) when rings B and C form tetrahydro-1H-(1,4-benzodiazepine, A is -C(O)NHOH, U is SO<sub>2</sub>, then Z is other than phenyl;
- (vii) when U is SO<sub>2</sub>, then Ua-Xa-Ya is other than -OCH<sub>2</sub>-C<sub>triple</sub>bondC-, -NHCH<sub>2</sub>-C<sub>triple</sub>bondC-, -CH<sub>2</sub>CH<sub>2</sub>-C<sub>triple</sub>bondC- or -SCH<sub>2</sub>-C<sub>triple</sub>bondC-;
- (viii) when U is SO<sub>2</sub> and Z is phenyl, then Ua is other than OC(O).

L51 ANSWER 6 OF 85 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN  
 ACCESSION NUMBER: 2004-080580 [08] WPIX  
 DOC. NO. CPI: C2004-033220  
 TITLE: New acetylenic ortho-sulfonamido and phosphinic acid amido bicyclic heteroaryl hydroxamic acids useful for treating graft rejection, HIV, atherosclerosis, restenosis, angiogenesis, tumor metastasis.  
 DERWENT CLASS: B05  
 INVENTOR(S): ALBRIGHT, J D; CHEN, J M; DU, X; LEVIN, J I; ZASK, A  
 PATENT ASSIGNEE(S): (AMCY) AMERICAN CYANAMID CO; (AMHP) WYETH HOLDINGS CORP  
 COUNTRY COUNT: 1  
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG MAIN IPC
US 2003208066	A1	20031106 (200408)*		36	C07D279-02
US 6946473	B2	20050920 (200562)			C07D471-04

## APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 2003208066	A1 Provisional Cont of	US 1999-198221P US 2000-492978 US 2003-390515	19990127 20000127 20030317

US 6946473	B2 Provisional	US 1999-198221P	19990127
	Cont of	US 2000-492978	20000127
		US 2003-390515	20030317

PRIORITY APPLN. INFO: US 1999-198221P      19990127; US  
                   2000-492978      20000127; US  
                   2003-390515      20030317

## INT. PATENT CLASSIF.:

MAIN: C07D279-02; C07D471-04  
 SECONDARY: A61K031-437; A61P019-02; C07D487-02; C07D491-02;  
              C07D498-02; C07D498-04; C07D513-04

## BASIC ABSTRACT:

US2003208066 A UPAB: 20040202  
 NOVELTY - Acetylenic ortho-sulfonamido and phosphinic acid amido bicyclic heteroaryl hydroxamic acids are new.

DETAILED DESCRIPTION - Acetylenic ortho-sulfonamido and phosphinic acid amido bicyclic heteroaryl hydroxamic acids of formulae (I)

- (IV) or their salts are new.

W and X = C or N;

P1 and Q = -N(R5)-G-L-Z-C(R6)(R7)-C equivalent to C-R8 or  
 -C(O)-NHOH;

Y = C, N, O or S;

G = SO<sub>2</sub> or P(O)R<sub>4</sub>;

L = phenyl, naphthyl or heteroaryl;

Z = O, NH, S or CH<sub>2</sub>;

A = phenyl ring or heteroaryl ring of formulae (i) - (iii), pyrazine or pyridine;

K1 = O, NR<sub>9</sub> or S;

R5 = H or 1-6C alkyl;

R6 and R7 = H, 1-6C alkyl, CN or CCH;

R8 = H, 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl, 3-6C cycloalkyl, phenyl, naphthyl or 5 - 10 membered heteroaryl (containing 1 - 3 N, NR<sub>9</sub>, O or S);

R9 = H, 1-6C alkyl, 3-6C cycloalkyl or phenyl.

Provided that:

(1) when P1 is -N(R5)-G-L-Z-C(R6)(R7)-C equivalent to C-R8, then Q is -C(O)-NHOH or vice-versa;

(2) at least one of W, X and Y is other than C; and

(3) G and Z are not bonded to adjacent atoms of L

An INDEPENDENT CLAIM is included for sulfonic acid derivatives of formula (XII) and (XIII).

R8a = 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl, 3-6C cycloalkyl, phenyl, naphthyl, 5 - 10 membered heteroaryl (containing 1 - 3 N, NR<sub>9</sub>, O or S), or 5 - 9 membered heterocycloalkyl (containing 1 or 2 N, NR<sub>9</sub>, O or S);

J = F, Cl, Br, 1,2,4-triazolyl, benzotriazolyl or imidazolyl.

ACTIVITY - Antirheumatic; Antiarthritic; Immunosuppressive;

Immunomodulator; Antinflammatory; Antipyretic; Antidiabetic; Cardiant; Anti-HIV; CNS-Gen.; Gastrointestinal-Gen.; Antiarteriosclerosis, Vasotropic; Antiangiogenic; Neuroprotective; Cytostatic; Osteopathic; Dermatological; Ophthalmological; Hepatotropic; Nephrotropic; Antibacterial; Antiulcer; Vulnerary.

MECHANISM OF ACTION - TNF-alpha

converting enzyme (TACE) inhibitor;

Matrix metalloproteinase (MMP-1/9/13)

inhibitor; Angiogenesis inhibitor.

The efficacy of 4((4-but-2-ynyoxy-benzenesulfonyl)-methyl-amino)-8-methoxy-quinoline-3-carboxylic acid hydroxyamide (T1) to inhibit TACE was evaluated by incubating T1 (10 μg/ml)

with **TACE** (10  $\mu$ M) in a solution containing Tris buffer (70  $\mu$ M) and 10% glycerol at room temperature for 10 minutes. A fluorescent peptidyl substrate (100  $\mu$ M) was then added to the reaction mixture. The reaction was evaluated by measuring the fluorescence. (T1) showed an IC<sub>50</sub> value of 17 nM.

**USE** - For inhibiting pathological changes mediated by **TNF- alpha converting enzyme (TACE)**; for treating rheumatoid arthritis, graft rejection, cachexia, inflammation, fever, insulin resistance, septic shock, congestive heart failure, inflammatory disease of the central nervous system, inflammatory bowel disease, HIV (claimed), atherosclerosis, restenosis, skin aging, angiogenesis, corneal ulceration, arthritis, tumor metastasis, tissue ulceration, abnormal wound healing, periodontal disease, bone disease, aneurysmal aortic disease, demyelinating diseases of central nervous system, cirrhosis of the liver, glomerular diseases of kidney, premature rupture of fetal membranes, age related macular degeneration, diabetic retinopathy, Sjogren's syndrome, ocular tumor, ocular angiogenesis.

**ADVANTAGE** - (I) exhibit enhanced levels of the inhibition of the **TACE** activity and selectivity over **matrix metalloproteinase** (e.g. **MMP-1**).

Dwg. 0/0

FILE SEGMENT: CPI

FIELD AVAILABILITY: AB; GI; DCN

MANUAL CODES: CPI: B05-B01E; B06-H; B14-A01; B14-A02B1; B14-C03;  
B14-C04; B14-C06; B14-C09; B14-E08; B14-E10;  
B14-F01; B14-F02; B14-F07; B14-G02; B14-G03;  
B14-H01B; B14-J01; B14-N01; B14-N03; B14-N10;  
B14-N12; B14-N17; B14-S04

TECH UPTX: 20040202

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: Preparation of (I) (where Q is  $-C(O)-NHOH$ , P1 is  $-N(R5)-G-L-Z-C(R6)(R7)-C$  equivalent to C-R8 and L is phenyl) involves converting carboxylic acid of formula (ia) into corresponding acid chloride or anhydride; or by reacting it with a peptide coupling agent, followed by reaction with hydroxylamine derivative to give (ib) and deprotection.

R30 = tert-butyl, benzyl, trialkylsilyl or other masking group.

ABEX UPTX: 20040202

SPECIFIC COMPOUNDS - 4((4-But-2-ynyoxy-benzenesulfonyl)-methyl-amino)-8-methoxy-quinoline-3-carboxylic acid hydroxyamide, 4((4-but-2-ynyoxy-benzenesulfonyl)-methyl-amino)-1,3-dimethyl-1H-pyrazolo(3,4-b)pyridine-5-carboxylic acid hydroxyamide, 4((4-but-2-ynyoxy-benzenesulfonyl)-methyl-amino)-3-methyl-isothiazolo(5,4-b)pyridine-5-carboxylic acid hydroxyamide, 8-bromo-4(((4-(2-butynyoxy)phenyl)sulfonyl)-(methyl)amino)-N-hydroxy-3-quinolinecarboxamide and 4-((4-but-2-ynyoxy-benzenesulfonyl)-methyl-amino)-3-methyl-isoxazolo(5,4-b)pyridine-5-carboxylic acid hydroxyamide are specifically claimed as (I).

ADMINISTRATION - Administration is by oral, intranasal, intramuscular, intraperitoneal, subcutaneous, intrabronchial or transdermal route. No dosage given.

EXAMPLE - To a solution of 4((4-but-2-ynyoxy-benzenesulfonyl)-methyl-amino)-8-methoxy-quinoline-3-carboxylic acid ethyl ester (0.82 g) in tetrahydrofuran (THF) (10 ml) and methanol (5 ml) was added 1N NaOH (2.15 ml) and the resultant mixture was refluxed for 3 hours. The resultant residue was triturated with ether to give 4((4-but-2-ynyoxy-benzenesulfonyl)-methyl-amino)-8-methoxy-quinoline-3-carboxylate salt (A1). To a solution of 2 M oxalyl chloride in dichloromethane (1.67 ml) was added dimethylformamide (DMF) (0.258 ml) and the reaction was stirred at 0 degrees C for 15 minutes. A solution of (A1) (0.75 g) in DMF was added

to the reaction mixture and stirred for 1 hour at room temperature. The resultant mixture was poured into a mixture of triethylamine (1.395 ml), THF (3 ml) and 50% aqueous solution of hydroxylamine (0.408 ml). The reaction was warmed at room temperature overnight and worked up to give 4((4-but-2-ynyloxy-benzenesulfonyl)-methyl-amino)-8-methoxy-quinoline-3-carboxylic acid hydroxyamide.

## DEFINITIONS - Preferred Definitions:

W and X = C;  
 P1 = -N(R5)-G-L-Z-C(R6)(R7)-Cequivalent toC-R8;  
 Q = -C(O)-NHOH;  
 Y = N;  
 G = SO<sub>2</sub>;  
 L = phenyl substituted at 1- and 4-positions by G and Z respectively;  
 Z = O;  
 R6 and R7 = H;  
 R8 = -CH<sub>2</sub>OH or methyl.

L51 ANSWER 7 OF 85 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN  
 ACCESSION NUMBER: 2003-456157 [43] WPIX  
 CROSS REFERENCE: 1999-312431 [26]; 2001-424086 [45]; 2001-656404 [75];  
 2002-146947 [19]  
 DOC. NO. CPI: C2003-121212  
 TITLE: New ortho-sulfonamido bicyclic heteroaryl  
 hydroxamic acids useful as matrix  
 metalloproteinase inhibitors for  
 treatment of diseases e.g. arthritis.  
 DERVENT CLASS: B05 D21  
 INVENTOR(S): ALBRIGHT, J D; DU, X; GU, Y; LEVIN, J I; ZASK, A  
 PATENT ASSIGNEE(S): (ALBR-I) ALBRIGHT J D; (DUXX-I) DU X; (GUYY-I) GU Y;  
 (LEVI-I) LEVIN J I; (ZASK-I) ZASK A; (AMCY) AMERICAN  
 CYANAMID CO  
 COUNTRY COUNT: 1  
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
US 2002132826	A1	20020919 (200343)*		39	A61K031-497	
US 6534491	B2	20030318 (200343)			C07D471-02	

## APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 2002132826	A1	US 2000-734146	20001211
US 6534491	B2 Provisional	US 1996-28505P	19961016
	CIP of	US 1997-944188	19971006
	CIP of	US 1998-55856	19980406
	Div ex	US 1998-59554	19980414
		US 2000-734146	20001211

## FILING DETAILS:

PATENT NO	KIND	PATENT NO
US 6534491	B2 Div ex	US 6228869

PRIORITY APPLN. INFO: US 2000-734146 20001211; US  
 1996-28505P 19961016; US  
 1997-944188 19971006; US

1998-55856	19980406; US
1998-59554	19980414

## INT. PATENT CLASSIF.:

MAIN: A61K031-497; C07D471-02  
 SECONDARY: A61K031-415; A61K031-44; A61K031-47; C07D207-00;  
 C07D217-00; C07D221-02; C07D491-02; C07D498-02;  
 C07D513-02; C07D515-02

## BASIC ABSTRACT:

US2002132826 A UPAB: 20030707

NOVELTY - Ortho-sulfonamido bicyclic heteroaryl hydroxamic acids (I) - (III) or their salts, are new.

DETAILED DESCRIPTION - Ortho-sulfonamido bicyclic heteroaryl hydroxamic acids of formula (I) - (III) or their salts, are new:

A = 5-6 membered phenyl or heteroaryl ring which may contain 0 - 2 heteroatoms selected from N, O or S (both optionally mono- to tri-substituted by R1);

R1 = H, halo, 1-8C alkyl, 2-6C alkenyl, 2-6C alkynyl, 3-6C cycloalkyl, -(CH<sub>2</sub>)<sub>n</sub>-Z, -OR<sub>2</sub>, -CN, COR<sub>2</sub>, 1-4C perfluoroalkyl, -CONR<sub>2</sub>R<sub>3</sub>, -S(O)<sub>x</sub>R<sub>2</sub>, -OP(O)(OR<sub>2</sub>)OR<sub>3</sub>, PO(OR<sub>2</sub>)OR<sub>3</sub>, OC(O)NR<sub>2</sub>R<sub>3</sub>, COOR<sub>2</sub>, -CONR<sub>2</sub>R<sub>3</sub>, SO<sub>3</sub>H, NR<sub>2</sub>R<sub>3</sub>, NR<sub>2</sub>COR<sub>3</sub>, NR<sub>2</sub>COOR<sub>3</sub>, SO<sub>2</sub>NR<sub>2</sub>R<sub>3</sub>, NO<sub>2</sub>, N(R<sub>2</sub>)SO<sub>2</sub>R<sub>3</sub>, NR<sub>2</sub>CONR<sub>2</sub>R<sub>3</sub>, NR<sub>2</sub>C(=NR<sub>3</sub>)NR<sub>2</sub>R<sub>3</sub>, SO<sub>2</sub>NHCOR<sub>4</sub>, CONHSO<sub>2</sub>R<sub>4</sub>, tetrazol-5-yl, SO<sub>2</sub>NHCN, SO<sub>2</sub>NHCONR<sub>2</sub>R<sub>3</sub> or Z;

x = 0 - 2;

n = 1 - 6;

R<sub>2</sub>, R<sub>3</sub> = H or L;

L = 1-8C alkyl, 2-6C alkenyl, 2-6C alkynyl, 3-6C cycloalkyl, 1-4C perfluoroalkyl, Z or V';

Z = heteroaryl (optionally fused with phenyl and containing 5 - 6 ring atoms and 1 - 3 heteroatoms selected from N, O or S), phenyl or naphthyl (all optionally mono- to tri-substituted by R1);

V' = saturated or partially unsaturated heterocycloalkyl ring of 5 - 7 ring atoms having 1 - 3 heteroatoms of N, O or S (optionally mono- or di-substituted by R2);

R<sub>4</sub> = L;

P, Q = -N(CH<sub>2</sub>-R<sub>5</sub>)-S(O)<sub>2</sub>-Z or -C(O)-NHOH;

R<sub>5</sub> = H, 1-8C alkyl, 2-6C alkenyl, 2-6C alkynyl, Z or V';

T, U, W, X = C or N;

Y = C, N, O or S; and

provided that:

(1) P and Q are not -N(CH<sub>2</sub>-R<sub>5</sub>)-S(O)<sub>2</sub>-Z or -C(O)-NHOH at the same time;

(2) when T and U are C, then both are optionally substituted by R1; and

(3) at least one of T, U, W, X and Y is not carbon and less than 2 of T, U, W and X are nitrogen.

ACTIVITY - Antiarthritic; Antirheumatic; Antiinflammatory; Immunosuppressive; Antipyretic; Antibacterial; Cardiant; Anti-HIV; Antiarteriosclerotic; Cytostatic; Antitumor; Vulnerary; Hepatotropic; Vasotropic; Antiulcer; Nephrotropic; Dermatological; Antidiabetic; Ophthalmological; Immunomodulator; CNS-Gen.; Osteopathic.

MECHANISM OF ACTION - Matrix metalloproteinase (MMP) (e.g. gelatinase, stromelysin and collagenase) inhibitors; TNF- alpha converting enzyme inhibitors.

Ac-Pro-Leu-Gly(2-mercaptop-4-methyl-pentanoyl)-Leu-Gly-OEt and (5,5'-dithiobis(2-nitrobenzoic acid)) (DTNB) were diluted together to 1 mM with a substrate buffer (50 mM HEPES, pH 7.5, 5 mM CaCl<sub>2</sub>). The stock of MMP-13 (collagenase) was also diluted with a substrate buffer (50 mM HEPES, pH 7.5, 5 mM CaCl<sub>2</sub>, 0.02% Brij) to a final concentration. The buffer, enzyme, vehicle or 4-(benzyl-(4-methoxy-benzenesulfonyl)-amino)-7-

trifluoromethyl-quinoline-3-carboxylic acid hydroxyamide (A) and DTNB/substrate were added in this order to a 96 well plate and the increase in color was monitored spectrophotometrically, from which IC<sub>50</sub> value was determined. (A) showed IC<sub>50</sub> of 7 nM for MMP-13.

USE - For inhibiting pathological changes (e.g. atherosclerosis, atherosclerotic plaque formation, reduction of coronary thrombosis from atherosclerotic plaque rupture, restenosis, MMP-mediated osteopenias, inflammatory diseases of the central nervous system, skin aging, angiogenesis, tumor metastasis, tumor growth, osteoarthritis, rheumatoid arthritis, septic arthritis, corneal ulceration, abnormal wound healing, bone disease, proteinuria, aneurysmal aortic disease, degenerative cartilage loss following traumatic joint injury, demyelinating diseases of the nervous system, cirrhosis of the liver, glomerular disease of the kidney, premature rupture of fetal membranes, inflammatory bowel disease or periodontal disease, age related macular degeneration, diabetic retinopathy, proliferative vitreoretinopathy, retinopathy of pre-maturity, ocular inflammation, keratoconus, Sjogren's syndrome, myopia, ocular tumor, ocular angiogenesis/neovascularization and corneal graft rejection) mediated by matrix metalloproteinase and changes (e.g. graft rejection, cachexia, anorexia, inflammation, fever, insulin resistance, septic shock, congestive heart failure, inflammatory diseases of the central nervous system, inflammatory bowel disease and HIV infection) mediated by TNF- alpha converting enzyme (TACE) in a mammal (claimed).

ADVANTAGE - The compounds are inhibitors of matrix metalloproteinases (e.g. gelatinases, stromelysins and collagenases) and TNF- alpha converting enzyme.

Dwg.0/0

FILE SEGMENT: CPI

FIELD AVAILABILITY: AB; GI; DCN

MANUAL CODES: CPI: B06-H; B14-A02B1; B14-C03; B14-C04; B14-C09; B14-D07C; B14-E10C; B14-E11; B14-F01; B14-F01B; B14-F01G; B14-F04; B14-F07; B14-G02C; B14-H01; B14-J01; B14-J01A2; B14-N01; B14-N03; B14-N06B; B14-N10; B14-N12; B14-N17; B14-S04; B14-S06; D08-B09A3

TECH UPTX: 20030707

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: The compounds are prepared by:  
 (1) reacting a bicyclic heteroaryl prepared from a corresponding aniline, with N-benzyl-para-methoxybenzenesulfonamide to form N,N-disubstituted sulfonamido-ester; and  
 (2) converting the ester.

ABEX UPTX: 20030707

SPECIFIC COMPOUNDS - 66 Compounds (I) - (III) are specifically claimed, e.g. 4-(benzyl-(4-methoxy-benzenesulfonyl)-amino)-7-trifluoromethyl-quinoline-3-carboxylic acid hydroxyamide.

ADMINISTRATION - The compounds can be administered orally in a dosage of (2 - 500, preferably 2 - 50, especially 5 - 25 mg/kg), nasally or parenterally (including intramuscular, intraperitoneal, or subcutaneous injection), intranasal or intrabronchial inhalation or insufflation, rectally, transdermally or as an aerosol.

EXAMPLE - Dimethylformamide (DMF) (0.05 ml) was added to a solution of 4-(benzyl-(4-methoxy-benzenesulfonyl)-amino)-7-trifluoromethyl-quinoline-3-carboxylic acid (0.636 g) in dichloromethane (12.5 ml), followed by addition of 2M oxalyl chloride (1.26 ml), and the resulting mixture was

stirred at room temperature for 1 hour. Triethylamine (2.6 ml) was added to a 0 degrees C mixture of hydroxylamine hydrochloride (350 mg) in tetrahydrofuran (14 ml) and water (3.5 ml). After this mixture was stirred for 15 minutes at 0 degrees C, the acid chloride solution was added to it in one portion and the resulting solution was warmed to room temperature and stirred for another 4 hours. Water was added to the reaction flask and 4-(benzyl-(4-methoxy-benzenesulfonyl)-amino)-7-trifluoromethyl-quinoline-3-carboxylic acid hydroxyamide (0.488 g, 75% yield) was collected.

**DEFINITIONS - Preferred Definitions:**

The compound is of formula (II).

W, X = C;

T = N;

U = C optionally substituted by R1;

P' = -N(CH<sub>2</sub>-R5)-S(O)<sub>2</sub>-Z;

Q = -C(O)-NHOH; and

T' = phenyl or pyrazole (both optionally mono- to tri-substituted by R1).

L51 ANSWER 8 OF 85 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN  
 ACCESSION NUMBER: 2002-146947 [19] WPIX  
 CROSS REFERENCE: 1999-312431 [26]; 2001-424086 [45]; 2001-656404 [75];  
 2003-456157 [43]  
 DOC. NO. CPI: C2002-045527  
 TITLE: New ortho-sulfonamido bicyclic heteroaryl hydroxamic acids are useful for treating diseases implicated by metalloproteinases and tumor necrosis factor-alpha e.g. atherosclerosis and restenosis.  
 DERWENT CLASS: B05  
 INVENTOR(S): ALBRIGHT, J D; DU, X; GU, Y; LEVIN, J I; ZASK, A  
 PATENT ASSIGNEE(S): (ALBR-I) ALBRIGHT J D; (DUXX-I) DU X; (GUYY-I) GU Y; (LEVI-I) LEVIN J I; (ZASK-I) ZASK A; (AMCY) AMERICAN CYANAMID CO  
 COUNTRY COUNT: 1  
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
US 2001046989	A1	20011129 (200219)*		39	A61K031-535	
US 6548524	B2	20030415 (200329)			A61K031-59	

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 2001046989	A1 Provisional	US 1996-28505P	19961016
	CIP of	US 1997-944188	19971006
		US 2000-734140	20001211
US 6548524	B2 Provisional	US 1996-28505P	19961016
	CIP of	US 1997-944188	19971006
	CIP of	US 1998-55856	19980406
	Div ex	US 1998-59554	19980414
		US 2000-734140	20001211

PRIORITY APPLN. INFO: US 1996-28505P 19961016; US  
 1997-944188 19971006; US  
 2000-734140 20001211; US  
 1998-55856 19980406; US

1998-59554

19980414

## INT. PATENT CLASSIF.:

MAIN: A61K031-535; A61K031-59  
 SECONDARY: C07D221-02; C07D471-02; C07D491-02; C07D498-02;  
 C07D513-02; C07D515-02

## BASIC ABSTRACT:

US2001046989 A UPAB: 20030707  
 NOVELTY - Ortho-sulfonamido bicyclic heteroaryl hydroxamic acids  
 (B) and their salts are new.

DETAILED DESCRIPTION - Ortho-sulfonamido bicyclic heteroaryl  
 hydroxamic acids of formula (B) and their salts are new.

(B) = compound of formula (Ia), (Ib) or (Ic);  
 P and Q = -N-(CH<sub>2</sub>-R<sub>5</sub>)-(SO<sub>2</sub>)-Z (II) or -C(=O)-NHOH (III);  
 T, U, W and X = C or N;  
 Y = C, N, O or S;  
 A = phenyl or 5-6 membered heteroaryl ring (containing 0 - 2  
 heteroatom selected from N, O or S in addition to any heteroatoms defined  
 by W or X and, is optionally mono-, di- or tri-substituted with R<sub>1</sub>);  
 Z = phenyl, naphthyl, M or M fused to phenyl (all optionally mono-,  
 di- or tri-substituted with R<sub>1</sub>);

M = heteroaryl moiety containing 5 - 6 ring atoms and 1 - 3  
 heteroatoms selected from N, O or S;  
 V = saturated or partially saturated heterocycloalkyl ring of 5 - 7  
 ring atoms having 1 - 3 heteroatoms selected from N, O or S (optionally  
 mono-, or di-substituted with R<sub>2</sub>);

R<sub>1</sub> = H, halo, 1-8C alkyl, 2-6C alkenyl, 2-6C alkynyl, 3-6C  
 cycloalkyl, -(CH<sub>2</sub>)<sub>n</sub>Z, -OR<sub>2</sub>, -CN, -COR<sub>2</sub>, 1-4C perfluoroalkyl, -CONR<sub>2</sub>R<sub>3</sub>,  
 -S(O)<sub>x</sub>R<sub>2</sub>, -OPO(OR)OR<sub>3</sub>, -PO(OR<sub>2</sub>)R<sub>3</sub>, -OC(O)NR<sub>2</sub>R<sub>3</sub>, -COOR<sub>2</sub>, -CONR<sub>2</sub>R<sub>3</sub>, -SO<sub>3</sub>H,  
 -NR<sub>2</sub>R<sub>3</sub>, -NR<sub>2</sub>COR<sub>3</sub>, -NR<sub>2</sub>COOR<sub>3</sub>, -SO<sub>2</sub>NR<sub>2</sub>R<sub>3</sub>, -NO<sub>2</sub>, -N(R<sub>2</sub>)SO<sub>2</sub>R<sub>3</sub>, -NR<sub>2</sub>CO, NR<sub>2</sub>R<sub>3</sub>,  
 -NR<sub>2</sub>C(=NR<sub>3</sub>)NR<sub>2</sub>R<sub>3</sub>, -SO<sub>2</sub>NHCOR<sub>4</sub>, -CONHSO<sub>2</sub>R<sub>4</sub>, -tetrazol-5-yl, -SO<sub>2</sub>NHCN,  
 -SO<sub>2</sub>NHCONR<sub>2</sub>R<sub>3</sub> or Z;  
 R<sub>2</sub> and R<sub>3</sub> = H or Z<sub>1</sub>;  
 Z<sub>1</sub> = 1-8C alkyl, 2-6C alkenyl, 2-6C alkynyl or 3-6C cycloalkyl, 1-4C  
 perfluoroalkyl, Z or V;

R<sub>4</sub> = Z<sub>1</sub>;  
 R<sub>5</sub> = H, 1-8C alkyl, 2-6C alkenyl, 2-6C alkynyl, Z or V;  
 n = 1 - 6; and  
 x = 0 - 2.

Provided that when T or U is carbon, either may be optionally  
 substituted with R<sub>1</sub>; and when P is (II), then Q is (III) or when P is  
 (III), Q is (II); and at least one of T, U, W, X and Y is not carbon and  
 than no more than 2 of T, U, W and X are nitrogen.

ACTIVITY - Antiarteriosclerotic; vasotropic; anti-inflammatory;  
 dermatological; osteopathic; antiarthritic; cytostatic; antirheumatic;  
 antiulcer; vulnerary; hepatotropic; nephrotropic; nootropic;  
 neuroprotective; antidiabetic; ophthalmological; keratolytic;  
 immunosuppressive; antipyretic; cardiant; antibacterial; anti-HIV.

MECHANISM OF ACTION - Tumor necrosis factor-  
 alpha converting enzyme (TACE)  
 inhibitor; Matrix metalloproteinases (MMP)  
 (preferably MMP-1, MMP-9 and MMP-13) inhibitor.

In tests for measuring in vivo MMP inhibitory action of (B), carried out on Sprague Dawley rats, 4-(pyridin-3-ylmethyl-(toluene-4-sulfonyl)-amino)-7-trifluoromethyl-quinoline-3-carboxylic acid hydroxyamide showed inhibition of 65% at 1 micro M concentration.

USE - For inhibiting pathological changes mediated by matrix metalloproteinase (MMP) and the condition mediated by MMP are atherosclerosis, atherosclerotic

plaque formation, reduction of coronary thrombosis from atherosclerotic plaque rupture, restenosis, MMP-mediated osteopenias, inflammatory diseases of the central nervous system, skin aging, angiogenesis, tumor metastasis, tumor growth, osteoarthritis, rheumatoid arthritis, septic arthritis, corneal ulceration, abnormal wound healing, bone disease, proteinuria, aneurysmal aortic disease, degenerative cartilage loss following traumatic joint injury, demyelinating diseases of the nervous system, cirrhosis of the liver, glomerular disease of the kidney, premature rupture of fetal membranes, inflammatory bowel disease or periodontal disease, age related macular degeneration, diabetic retinopathy, proliferative vitreoretinopathy, retinopathy of prematurity, ocular inflammation, keratoconus, Sjogren's syndrome, myopia, ocular tumors, ocular angiogenesis/neovascularization and corneal graft rejection; also for inhibiting pathological changes mediated by tumor necrosis factor (TNF) - alpha converting enzyme (TACE) e.g. rheumatoid arthritis, graft rejection, cachexia, anorexia, inflammation, fever, insulin resistance, septic shock, congestive heart failure, inflammatory disease of the central nervous system, inflammatory bowel disease or HIV infection (all claimed).

Dwg.0/0

FILE SEGMENT: CPI

FIELD AVAILABILITY: AB; GI; DCN

MANUAL CODES: CPI: B06-H; B14-A01; B14-A02B1; B14-C04; B14-C06; B14-C09; B14-D07C; B14-E10C; B14-E11; B14-F01B; B14-F01G; B14-F02; B14-F07; B14-G02C; B14-J01; B14-N03; B14-N10; B14-N12; B14-N16; B14-N17B; B14-N17C; B14-P03; B14-S04; B14-S06

TECH UPTX: 20021113

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: (B) is prepared e.g. by reaction of 4-chloro-7-trifluoromethylquinoline-3-carboxylic acid ethyl ester with R7-NH<sub>2</sub>, and the resulting 4-(R7-amino)quinoline carboxylic acid ester is then reacted with the appropriate Z-SO<sub>2</sub>-Cl. Hydrolysis of the ester and reaction with hydroxylamine hydrochloride yields a compound of (B).

ABEX UPTX: 20021113

SPECIFIC COMPOUNDS - 66 Compounds (I) are specifically claimed e.g. 4-(benzyl-(4-methoxy-benzenesulfonyl)-amino)-7-trifluoromethyl-quinoline-3-carboxylic acid hydroxyamide (I').

ADMINISTRATION - The compound may be administered by intramuscular, intraperitoneal, subcutaneous, intravenous, oral, intranasal or intrabronchial inhalation or insufflation route or transdermal route. For oral route, the daily dosage is 2 - 500 (preferably 5 - 25) mg/kg.

EXAMPLE - To a solution of 4-(benzyl-(4-methoxy-benzenesulfonyl)-amino)-7-trifluoromethyl-quinoline-3-carboxylic acid (0.636 g) in dichloromethane (12.5 ml) was added dimethyl formamide (0.05 ml) followed by 2M oxalyl chloride (1.26 ml). The resulting mixture was stirred at room temperature for 1 hour. In a flask, triethylamine (2.6 ml) was added to a 0 degrees C mixture of hydroxylamine hydrochloride (350 mg) in tetrahydrofuran (14 ml) and water (3.5 ml). After this mixture had been stirred for 15 minutes at 0 degrees C, the acid chloride solution was added to it in one portion. The resulting solution was warmed to room temperature and stirred for 4 hours. Water was then added to the reaction flask to obtain 4-(benzyl-(4-methoxy-benzenesulfonyl)-amino)-7-trifluoromethyl-quinoline-3-carboxylic acid hydroxyamide (I'; 75%).

DEFINITIONS - Preferred Definitions:

(B) = formula (Ib);

W and X = C;  
 U = C optionally substituted with R1;  
 P = formula (II);  
 Q = formula (III); and  
 A = phenyl of pyrazole ring optionally mono-, di- or tri-substituted with R1.

L51 ANSWER 9 OF 85 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN  
 ACCESSION NUMBER: 2001-656404 [75] WPIX  
 CROSS REFERENCE: 1999-312431 [26]; 2001-424086 [45]; 2002-146947 [19];  
 2003-456157 [43]  
 DOC. NO. CPI: C2001-193023  
 TITLE: New bicyclic heteroaryl hydroxamic acids are matrix metalloproteinase inhibitor and tumor necrosis factor-alpha converting enzyme inhibitors, useful in the treatment of e.g. arteriosclerosis, inflammation, arthritis and tumors.  
 B02 B03  
 DERWENT CLASS:  
 INVENTOR(S): ALBRIGHT, J D; DU, X; GU, Y; LEVIN, J I; ZASK, A  
 PATENT ASSIGNEE(S): (ALBR-I) ALBRIGHT J D; (DUXX-I) DU X; (GUYY-I) GU Y; (LEVI-I) LEVIN J I; (ZASK-I) ZASK A; (AMCY) AMERICAN CYANAMID CO  
 COUNTRY COUNT: 1  
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
US 2001025047	A1	20010927	(200175)*		40	C07D215-12
US 6498167	B2	20021224	(200303)			A61K031-56

## APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 2001025047	A1 Provisional	US 1996-28505P	19961016
	CIP of	US 1997-944188	19971006
	CIP of	US 1998-55856	19980406
	Div ex	US 1998-59554	19980414
		US 2000-734056	20001211
US 6498167	B2 Provisional	US 1996-28505P	19961016
	CIP of	US 1997-944188	19971006
	CIP of	US 1998-55856	19980406
	Div ex	US 1998-59554	19980414
		US 2000-734056	20001211

## FILING DETAILS:

PATENT NO	KIND	PATENT NO
US 2001025047	A1 Div ex	US 6228869
US 6498167	B2 Div ex	US 6228869

PRIORITY APPLN. INFO: US 1996-28505P 19961016; US  
 1997-944188 19971006; US  
 1998-55856 19980406; US  
 1998-59554 19980414; US  
 2000-734056 20001211

INT. PATENT CLASSIF.:  
 MAIN: A61K031-56; C07D215-12

SECONDARY: A61K031-4709; C07D215-14; C07D217-00

BASIC ABSTRACT:

US2001025047 A UPAB: 20030707

NOVELTY - Bicyclic heteroaryl **hydroxamic** acids are new.

DETAILED DESCRIPTION - Bicyclic heteroaryl **hydroxamic** acids of formula (Ia), (Ib) and (Ic) and their salts are new.

P, Q = -N(CH<sub>2</sub>-R<sub>5</sub>)-S(=O)2-Z or -C(O)-NHOH;

T, U, W, X = C or N;

Y = C, N, S or O;

A = phenyl or A' (both optionally substituted by 1-3 R<sub>1</sub>);

A' = 5-6 membered heteroaryl ring containing 0-2 N, O or S;

Z = phenyl, naphthyl, A' or A' fused to phenyl (all optionally substituted by 1-3 R<sub>1</sub>);

R<sub>1</sub> = H, halo, 1-8C alkyl, 2-6C alkenyl, 2-6C alkynyl, 3-6C cycloalkyl, -(CH<sub>2</sub>)<sub>n</sub>Z, -OR<sub>2</sub>, -CN, -COR<sub>2</sub>, 1-4C perfluoroalkyl, -CONR<sub>2</sub>R<sub>3</sub>, -S(O)xR<sub>2</sub>, -OPO(OR<sub>2</sub>)OR<sub>3</sub>, -PO(OR<sub>2</sub>)R<sub>3</sub>, -OC(O)NR<sub>2</sub>R<sub>3</sub>, -COOR<sub>2</sub>, -CONR<sub>2</sub>R<sub>3</sub>, -SO<sub>3</sub>H, -NR<sub>2</sub>R<sub>3</sub>, -NR<sub>2</sub>COR<sub>3</sub>, -NR<sub>2</sub>COOR<sub>3</sub>, -SO<sub>2</sub>NR<sub>2</sub>R<sub>3</sub>, -NO<sub>2</sub>, -N(R<sub>2</sub>)SO<sub>2</sub>R<sub>3</sub>, -NR<sub>2</sub>ONR<sub>2</sub>R<sub>3</sub>, -NR<sub>2</sub>C(=NR<sub>3</sub>)NR<sub>2</sub>R<sub>3</sub>, -SO<sub>2</sub>NHCOR<sub>4</sub>, -CONHSO<sub>2</sub>R<sub>4</sub>, -tetrazol-5-yl, -SO<sub>2</sub>NHCN, -SO<sub>2</sub>NHCONR<sub>2</sub>R<sub>3</sub> or Z;

V = saturated or partially unsaturated 5-7 membered heterocycloalkyl ring containing 1-3 N, O or S (optionally substituted by 1-2 R<sub>2</sub>);

R<sub>2</sub>, R<sub>3</sub> = H, 1-8C alkyl, 2-6C alkenyl, 2-6C alkynyl, 3-6C cycloalkyl, 1-4C perfluoroalkyl, Z or V;

R<sub>4</sub> = 1-8C alkyl, 2-6C alkenyl, 2-6C alkynyl, 3-6C cycloalkyl, 1-4C perfluoroalkyl, Z or V;

n = 1-6; and

x = 0-2;

provided that when T and U = C, then either may be optionally substituted by R<sub>1</sub>; at least one of T, U, W, X and Y is not C, and no more than 2 of T, U, W and X = N; and when P = -N(CH<sub>2</sub>-R<sub>5</sub>)-S(=O)2-Z, then Q = -C(O)-NHOH and vice versa.

ACTIVITY - Antiarteriosclerotic; Thrombolytic; Cardiant; Vasotropic; Osteopathic; Antiinflammatory; Cerebroprotective; Neuroprotective; Dermatological; Cytostatic; Antiarthritic; Antirheumatic; Antibacterial; Ophthalmological; Antiulcer; Vulnerary; Hepatotropic; Nephrotropic; Antidiabetic; Gastrointestinal; Immunosuppressive; Anabolic; Immunomodulator; Antipyretic; Virucide; Anti-HIV.

MECHANISM OF ACTION - Matrix metalloproteinase (MMP) inhibitor; Tumor necrosis factor-alpha (TNF-alpha) converting enzyme (TACE) inhibitor.

A 2 cm piece of dialysis tubing containing MMP-1 (stromelysin), MMP-13 (collagenase) or MMP-9 (gelatinase) in buffer (0.5 ml) was implanted to Sprague-Dawley rat. 4-((4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino)-8-methoxy-quinoline-3-carboxylic acid hydroxyamide (I') (0.1 - 0.25 ml) was administered through a cannula in the jugular vein. Contents of the dialysis tubing was collected and enzyme activity assayed. 4-((4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino)-8-methoxy-quinoline-3-carboxylic acid hydroxyamide (I') displayed IC<sub>50</sub> values of 46, 2 and 1 nM against MMP-1, MMP-9 and MMP-13 respectively.

USE - In the treatment of atherosclerosis, atherosclerotic plaque formation, reduction of coronary thrombosis from atherosclerotic plaque rupture, restenosis, osteopenias, inflammatory diseases of the central nervous system, skin aging, angiogenesis, tumor metastasis, tumor growth, osteoarthritis, rheumatoid arthritis, septic arthritis, corneal ulceration, abnormal wound healing, bone disease, proteinuria, aneurysmal aortic disease, degenerative cartilage loss following traumatic joint injury, demyelinating disease of the nervous system, cirrhosis of the

liver, glomerular disease of the kidney, premature rupture of fetal membranes, inflammatory bowel disease, periodontal disease, age related macular degeneration, diabetic retinopathy, proliferative vitreoretinopathy, retinopathy of prematurity, ocular inflammation, keratoconus, Sjogrens syndrome, myopia, ocular tumor, ocular angiogenesis/neovascularization, corneal graft rejection, cachexia, anorexia, inflammation, fever, insulin resistance, septic shock, congestive heart failure and HIV infection (all claimed).

ADVANTAGE - The compounds are long-acting and orally bioavailable.

Dwg.0/0

FILE SEGMENT:

CPI

FIELD AVAILABILITY:

AB; GI; DCN

MANUAL CODES:

CPI: B05-B01E; B05-B01M; B06-H; B14-A02B1; B14-C03;  
B14-C04; B14-C09; B14-D07C; B14-E10C; B14-E11;  
B14-F01B; B14-F02D; B14-F04; B14-F07; B14-G02C;  
B14-H01; B14-J01; B14-J05B; B14-L06; B14-N01;  
B14-N03; B14-N06B; B14-N10; B14-N12; B14-N17;  
B14-P03; B14-S01; B14-S06

TECH

UPTX: 20011220

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: 11 Methods of preparing the compounds are disclosed, e.g. reacting quinoline carboxylic acid ester with an amine, and further with appropriate Z-SO<sub>2</sub>-Cl. Hydrolysis of the ester and reaction with hydroxylamine hydrochloride forms (I).

ABEX

UPTX: 20011220

SPECIFIC COMPOUNDS - 66 Compounds (I) are specifically claimed e.g. 4-((4-Methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino)-8-methoxy-quinoline-3-carboxylic acid hydroxyamide (I').

ADMINISTRATION - Administration of (I) is 2-500, preferably 5-25 mg/kg/day orally. (I) May also be administered intramuscularly, intraperitoneally, subcutaneously, intranasally, by intrabronchial inhalation or transdermally.

EXAMPLE - To a solution of 4-chloro-8-methoxy-3-quinolinicarboxylate (2 mmol) in methanol/tetrahydrofuran (THF) (1:1) (4 ml) was added 1 N sodium hydroxide solution and the resulting mixture was stirred at 25 degrees C for 18 hours to form a carboxylic acid (A). To a solution of (A) (1.26 mmol) in dichloromethane (12.5 ml) was added dimethylformamide (0.05 ml) followed by 2 M oxalyl chloride (1.26 ml) and the mixture was stirred at room temperature for 1 hour. In a separate flask, triethylamine (2.6 ml) was added to a 0 degrees C mixture of hydroxylamine hydrochloride (350 mg) in THF (14 ml) and water (3.5 ml). After this mixture had been stirred for 15 minutes at 0 degrees C, the acid chloride solution was added to it and the resulting solution was allowed to warm to room temperature and stirred for another 4 hours to form 4-((4-Methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino)-8-methoxy-quinoline-3-carboxylic acid hydroxyamide (I').

DEFINITIONS - Preferred Definitions:

W, X = C;

T = N;

U = C optionally substituted by R1;

P = -N(-CH<sub>2</sub>-R5)-S(=O)<sub>2</sub>-Z;

Q = -C(O)NHOH;

A = phenyl or pyrazole (both optionally substituted by 1-3 R1).

L51 ANSWER 10 OF 85 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN

ACCESSION NUMBER: 2001-424086 [45] WPIX

CROSS REFERENCE: 1999-312431 [26]; 2001-656404 [75]; 2002-146947 [19];  
2003-456157 [43]

DOC. NO. CPI: C2001-128285  
 TITLE: New ortho-sulfonamido bicyclic hydroxamic acids, useful as antiarthritic agents having matrix metalloproteinase and TACE inhibiting action.  
 DERVENT CLASS: B02  
 INVENTOR(S): ALBRIGHT, J D; DU, X; GU, Y; LEVIN, J I; ZASK, A  
 PATENT ASSIGNEE(S): (AMCY) AMERICAN CYANAMID CO  
 COUNTRY COUNT: 1  
 PATENT INFORMATION:

PATENT NO	KIND DATE	WEEK	LA	PG MAIN IPC
US 6228869	B1 20010508 (200145)*			31 A61K031-47

## APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 6228869	B1 Provisional	US 1996-28505P	19961016
	CIP of	US 1997-944188	19971006
	CIP of	US 1998-55856	19980406
		US 1998-59554	19980414

PRIORITY APPLN. INFO: US 1996-28505P 19961016; US  
 1997-944188 19971006; US  
 1998-55856 19980406; US  
 1998-59554 19980414

## INT. PATENT CLASSIF.:

MAIN: A61K031-47  
 SECONDARY: C07D215-38; C07D217-00

## BASIC ABSTRACT:

US 6228869 B UPAB: 20030707

NOVELTY - Ortho-sulfonamido bicyclic hydroxamic acids (I) and their salts are new.

DETAILED DESCRIPTION - Ortho-sulfonamido bicyclic hydroxamic acids of formula (I) and their salts are new.

P, Q = group of formula (i) or (ii); provided that when P is (i) then Q is (ii) and vice versa;

W, X = C;

T, U = N or C; provided that when T is N then U is C, when T is C then U is N and when T or U is C, either may be optionally substituted;

W and X with the ring = phenyl optionally mono-, di- or tri-substituted with R1;

Z = phenyl, naphthyl, heteroaryl containing 5-6 ring atoms and 1-3 heteroatoms selected from N, O or S, optionally fused to phenyl, the phenyl, naphthyl, heteroaryl may be optionally mono-, di- or tri-substituted with R1;

R1 = H, halo, 1-8C alkyl, 2-6C alkenyl, 2-6C alkynyl, 3-6C cycloalkyl, (CH<sub>2</sub>)<sub>n</sub>Z, OR<sub>2</sub>, CN, COR<sub>2</sub>, 1-4C perfluoroalkyl, CONR<sub>2</sub>R<sub>3</sub>, S(O)<sub>x</sub>R<sub>2</sub>, OPO(OR<sub>2</sub>)OR<sub>3</sub>, PO(OR<sub>3</sub>)R<sub>3</sub>, OC(O)NR<sub>2</sub>R<sub>3</sub>, COOR<sub>2</sub>, CONR<sub>2</sub>R<sub>3</sub>, SO<sub>2</sub>H, NR<sub>2</sub>R<sub>1</sub>, NR<sub>2</sub>COR<sub>3</sub>, NR<sub>3</sub>COOR<sub>3</sub>, SO<sub>2</sub>NR<sub>2</sub>R<sub>3</sub>, NO<sub>2</sub>, N(R<sub>2</sub>), SO<sub>2</sub>R<sub>3</sub>, NR<sub>2</sub>CONR<sub>2</sub>R<sub>2</sub>, NR<sub>3</sub>C(=NR<sub>3</sub>)NR<sub>2</sub>R<sub>2</sub>, SO<sub>2</sub>NHCOR<sub>1</sub>, CONHSO<sub>2</sub>R<sub>1</sub>, tetrazol-5-yl, SO<sub>2</sub>NHCN, SO<sub>2</sub>NHCONR<sub>2</sub>R<sub>1</sub>, or Z;

V = saturated or partially unsaturated heterocycloalkyl ring of 5-7 ring atoms with 1-3 heteroatoms selected from N, O, or S, optionally mono-, di- substituted with R2;

R<sub>2</sub>, R<sub>3</sub> = H, 1-8C alkyl, 2-6C alkenyl, 2-6C alkynyl, 3-6C cycloalkyl, 1-4C perfluoroalkyl, Z or V;

R<sub>4</sub> = 1-8C alkyl, 2-6C alkenyl, 2-6C alkynyl, 3-6C cycloalkyl, 1-4C

perfluoroalkyl, Z or V;

R5 = H, 1-8C alkyl, 2-6C alkenyl, 2-6C alkynyl, Z or V;

n = 1-6; and

x = 0-2.

ACTIVITY - Antiarthritic; Cytostatic; Antiucler; Vulnerary; antiinflammatory; Immunosuppressive; osteopathic; Anti-HIV; Antiarteriosclerotic; Cerebroprotective; antirheumatic; antibacterial; Hepatotrophic; Nephrotropic; Antidiabetic; Ophthalmological.

MECHANISM OF ACTION - Matrix metalloproteinase (MMP)-1, MMP-9, MMP-13 and TNF-alpha converting enzyme (TACE) inhibitors.

MMP inhibition was tested in-vivo on a rat (Sprague-Dawley, 150-200 g) or mouse (CD-1, 25-50 g) which were administered with the specific drugs, 4-((4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino)-8-methoxy-quinoline-3-carboxylic acid hydroxyamide (Ia) showed an inhibition of 81% (50 mg/kg dose) p.o. versus MMP-13.

USE - (I) are useful in the treatment of arthritis, tumor metastasis, tissue ulceration, abnormal wound healing, periodontal disease, graft rejection, insulin resistance, bone disease and HIV infection. They are also useful in treating or inhibiting pathological changes mediated by MMPs such as atherosclerosis, atherosclerotic osteopenias, inflammatory disease of the central nervous system, skin aging, angiogenesis, tumor metastasis, tumor growth, osteoarthritis, rheumatoid arthritis, septic arthritis, corneal ulceration, proteinuria, aneurysmal aortic disease, degenerative cartilage loss following traumatic joint injury, demyelinating diseases of the nervous system, cirrhosis of the liver, glomerular disease of the kidney, premature rupture of fetal membranes, inflammatory bowel disease, age related muscular degeneration, diabetic retinopathy, proliferative vitreoretinopathy, retinopathy of prematurity, ocular inflammation, keratoconus, Sjogren's syndrome, myopia, ocular tumors, ocular angiogenesis/neovascularization and corneal graft rejection.

Dwg.0/0

FILE SEGMENT: CPI

FIELD AVAILABILITY: AB; GI; DCN

MANUAL CODES: CPI: B06-D02; B06-D03; B07-H; B10-J02; B14-A02B1; B14-C03; B14-C09; B14-D03; B14-D07C; B14-E08; B14-E10C; B14-G02C; B14-H01; B14-J05B; B14-N01; B14-N03; B14-N06B; B14-N10; B14-N12; B14-S01; B14-S04

TECH UPTX: 20010813

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: The 4-chloroquinoline carboxylic acid ester could be first reacted with R7-NH<sub>2</sub> and the resulting 4-(R7-amino)quinoline carboxylic acid ester then reacted with the appropriate Z-SO<sub>2</sub>-Cl. Hydrolysis of the ester and reaction with hydroxylamine hydrochloride would then give the desired product.

ABEX UPTX: 20010813

WIDER DISCLOSURE - Ortho-sulfonamido bicyclic hydroxamic acids of formula (I), (II) and (III) and their salts are new. Y' = C, N, O or S (provided that at least one of T, U, W, X and Y' is not C and further provided that no more than 2 of T, U, W and X are N); and W and X with the ring = phenyl or 5-6-membered heteroaryl ring containing 0-2 of N, O or S in addition to W and X.

SPECIFIC COMPOUNDS - 25 compounds are specifically claimed e.g. 4-((4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino)-8-methoxy-quinoline-3-carboxylic acid hydroxyamide of formula (Ia).

**ADMINISTRATION** - Projected oral daily dosages are 2-500 mg/kg, preferred oral daily dosages are 2-50 mg/kg and more preferred oral daily dosages are 5-25 mg/kg.

**EXAMPLE** - To a solution of 4-(benzyl-(4-methoxy-benzenesulfonyl)-amino)-7-trifluoromethylquinoline-3-carboxylic acid (0.636 g) in dichloromethane (12.5 ml) was added dimethylformamide (0.05 ml) followed by 2M oxalyl chloride (1.26 ml) and stirred at room temperature for 1 hour. In a separate flask triethylamine (2.6 ml) was added to a 0degreesC mixture of hydroxylamine hydrochloride (350 mg) in tetrahydrofuran (14 ml) and water (3.5 ml). After stirring for 15 minutes at 0degreesC the acid chloride solution was added to it in one portion and the resulting solution was allowed to warm to room temperature and stirred for another 4 hours. Water was then added to the reaction flask and 4-(benzyl-(4-methoxy-benzenesulfonyl)-amino)-7-trifluoromethylquinoline-3-carboxylic acid hydroxyamide (0.488 g) was collected via filtration.

L51 ANSWER 11 OF 85 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN  
 ACCESSION NUMBER: 2000-564722 [52] WPIX  
 DOC. NO. CPI: C2000-168195  
 TITLE: New N-(carboxyalkyl)-N-(biarylsulfonyl)glycyl hydroxamic acids, useful for treating e.g. arthritis, cancer, ulcers, periodontal disease, bone resorption, autoimmune disorders and AIDS.  
 DERWENT CLASS: B05  
 INVENTOR(S): ROBINSON, R P  
 PATENT ASSIGNEE(S): (PFIZ) PFIZER INC  
 COUNTRY COUNT: 1  
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN	IPC
US 6107337	A	20000822 (200052)*		14		A61K031-35	

**APPLICATION DETAILS:**

PATENT NO	KIND	APPLICATION	DATE
US 6107337	A	US 1998-130922	19980806

PRIORITY APPLN. INFO: US 1998-130922 19980806

INT. PATENT CLASSIF.:

MAIN: A61K031-35

SECONDARY: A61K031-216; A61K031-50; A61K031-5375

BASIC ABSTRACT:

US 6107337 A UPAB: 20001018

NOVELTY - N-(Carboxyalkyl)-N-(biarylsulfonyl)glycyl hydroxamic acids (I) and their salts are new

DETAILED DESCRIPTION - N-(Carboxyalkyl)-N-(biarylsulfonyl)glycyl hydroxamic acids of formula (I) and their salts are new:

Ar = 6-10C aryl-6-10C aryl;

n = 1-6;

X = hydroxy, 1-6C alkoxy, or NR1R2;

R1, R2 = H, 1-6C alkyl, piperidyl, 1-6C alkylpiperidyl, Y-piperidyl, Y-(1-6C alkylpiperidyl), 1-6C acylpiperidyl, Y, Y-(1-6C alkyl), 6-10C aryl 6-10C aryl, 6-10C aryl 6-10C aryl 1-6C alkyl, 3-6C alkyl, 3-6C cycloalkyl 1-6C alkyl, R5-(2-6C alkyl), R6-(1-6C alkyl), 1-5C alkyl (CH(R6) 1-6C alkyl), or CH(R7)COR8;

$Y = 6\text{-}10\text{C aryl or } 2\text{-}9\text{C heteroaryl};$   
 provided that, when one of  $R_1, R_2 = \text{CH}(R_7)\text{COR}_8$ , the other is H, 1-6C alkyl, or benzyl;

$R_5 = \text{hydroxy, or } 1\text{-}6\text{C alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, acyloxy or acylamino, } 6\text{-}10\text{C arylthio, arylsulfinyl, or arylsulfonyl, amino, mono- or di- (1-6C alkyl)amino, piperazinyl, (1-6C acyl)piperazinyl, (1-6C alkyl)piperazinyl } Y\text{-}(1-6\text{C alkyl})\text{piperazinyl, morpholinyl, thiomorpholinyl, piperidyl, or pyrrolidyl;}$

$R_6 = \text{piperidyl, (1-6C alkyl)piperidyl, } Y\text{-piperidyl, or } Y\text{-}(1-6\text{C alkyl)piperidyl;}$

$R_7 = \text{H, 1-6C alkyl, aminoalkyl, or hydroxyalkyl, } Y\text{-}(1-6\text{C alkyl), 1-6\text{C alkylthio 1-6C alkyl, 6-10\text{C arylthio 1-6C alkyl, 1-6C alkylsulfinyl 1-6C alkyl, 6-10\text{C arylsulfinyl 1-6C alkyl, mono- or di- (1-6C alkyl)amino 1-6C alkyl, R9R10NCO(1-6C alkyl), or R9OCO(1-6C alkyl);}$

$R_8 = \text{OR}_{11} \text{ or NR}_{11}\text{R}_{12};$

$R_9, R_{10}, R_{11}, R_{12} = \text{H, 1-6C alkyl, or } Y\text{-}(1-6\text{C alkyl); or R}_{1+R_2}, R_{9+R_{10}}, R_{11+R_{12}} = \text{azetidinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, indolinyl, isoindolinyl, piperazinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, (1-6C acyl)piperazinyl, (1-6C alkyl)piperazinyl, Q-piperazinyl, or a bridged diazabicycloalkyl group of formula (a)-(e):}$

$r = 1\text{-}3;$

$m = 1 \text{ or } 2;$

$p = 0 \text{ or } 1;$

$Q = \text{H, 1-3C alkyl, or 1-6C acyl;}$

$R_3, R_4 = \text{H, 1-6C alkyl or hydroxyalkyl, CF}_3, \text{CF}_3(1-6\text{C alkyl), 1-6C alkyl-(CF}_2), 1-3\text{C alkyl-(CF}_2)(1-3\text{C alkyl), Y, } Y\text{-}(1-6\text{C alkyl), 6-10\text{C aryl 6-10\text{C aryl 1-6C alkyl, 3-6C cycloalkyl, 3-6C cycloalkyl 1-6C alkyl, 1-6C acyloxy 1-6C alkyl, 1-6C alkoxy 1-6C alkyl, piperazinyl 1-6C alkyl, 1-6C acylamino 1-6C alkyl, piperidyl, (1-6C alkyl)piperidyl, } Y\text{-}(1-6\text{C alkoxy) 1-6C alkyl, 1-6C alkylthio 1-6C alkyl, 6-10\text{C arylthio 1-6C alkyl, 1-6C alkylsulfinyl 1-6C alkyl, 6-10\text{C arylsulfinyl 1-6C alkyl, 1-6C alkylsulfonyl 1-6C alkyl, 6-10\text{C arylsulfonyl 1-6C alkyl, 1-6C aminoalkyl, mono- or di- (1-6C alkyl)amino 1-6C alkyl, R13CO-(1-6C alkyl), or R14(1-6C alkyl);}$

$R_{13} = \text{OR}_{20} \text{ or NR}_{20}\text{R}_{21};$

$R_{14} = 1\text{-}6\text{C acylpiperazinyl, } Y\text{-piperazinyl, (1-6C alkyl)piperazinyl, morpholinyl, thiomorpholinyl, piperidinyl, pyrrolidinyl, piperidyl, (1-6C alkyl)piperidyl, } Y\text{-piperidyl, or (1-6C acyl)piperidyl; or}$

$R_{3+R_4}, R_{20+R_{21}} = 3\text{-}6\text{C cycloalkyl, tetrahydropyranyl, tetrahydropyranol, indanyl, tetrahydronaphthyl, or R15-(piperidyl); and R15 = H, 1-6C acyl or alkyl or alkylsulfonyl, or } Y\text{-}(1-6\text{C alkyl).}$

ACTIVITY - Cytostatic; osteopathic; antiarthritic; antirheumatic; vulnerary; vasotropic; antiarteriosclerotic; neuroprotective; ophthalmological; anti-HIV; antibacterial; immunosuppressive.

MECHANISM OF ACTION - (I) are matrix metalloproteinase (MMP) inhibitors, particularly of MMP-13, and inhibitors of tumor necrosis factor (TNF) production.

In MMP inhibition tests, 3-((4'-fluorobiphenyl-4-sulfonyl)-(1-hydroxycarbamoylcyclopentyl)amino)propionic acid, methyl ester (Ib) had IC<sub>50</sub> against human MMP-1 (collagenase) of 80 nM and against MMP-13 of 10 nM; the corresponding IC<sub>50</sub> values for the corresponding acid were 195 and 1.7 nM respectively.

USE - For treating MMP and TNF modulated disorders, including osteo- and rheumatoid arthritis, cancer including metastasis and invasion, tissue (e.g., corneal, gastric, and gastric) ulceration, abnormal wound healing, restenosis, periodontal disease,

epidermolysis bullosa, restenosis, bone resorption, loosening of artificial joint implants, osteoporosis, Paget's disease, atherosclerosis, multiple sclerosis, ocular angiogenesis leading to e.g., macular degeneration, HIV infection, AIDS, sepsis, and septic shock.

Dwg.0/0

FILE SEGMENT: CPI

FIELD AVAILABILITY: AB; GI; DCN

MANUAL CODES: CPI: B06-H; B07-H; B10-A08; B14-C09; B14-D07C; B14-F02D; B14-F07; B14-G01B; B14-H01; B14-L06; B14-N01; B14-N03; B14-N06B; B14-N17; B14-S01; B14-S06

TECH UPTX: 20001018

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: (I) are prepared by successive arylsulfonylation and N-alkylation of glycine esters, followed by conversion of the ester group into hydroxamic acid.

ABEX UPTX: 20001018

SPECIFIC COMPOUNDS - 4 Compounds (I) are specifically claimed, e.g.: 3-((4'-fluorobiphenyl-4-sulfonyl)-(1-hydroxycarbamoylcyclopentyl)amino)pro pionic acid (Ia) and its methyl ester (Ib).

ADMINISTRATION - Administration is e.g. oral, topical or parenteral. Dosage is 0.1-25 (preferably 0.3-5) mg/kg/day.

EXAMPLE - 1-Aminocyclopentanecarboxylic acid was converted into 1-((4'-fluorobiphenyl-4-sulfonyl)-(2-methoxycarbonylethyl)amino)cyclopenta necarboxylic acid benzyl ester by standard acylation and alkylation procedures with appropriate protections, and the benzyl group removed by hydrogenation in 100% yield. The acid (10.1 g) in DMF (170 ml) was treated with (i-Pr)2NET (4.3 ml) followed by BOP reagent (11.0 g) for 4 hours. More (i-Pr)2NET (7.8 ml) and O-benzylhydroxylamine HCl (4.64 g) were added, and the mixture stirred at 60degreesC for 16 hours. Work-up was by evaporation and EtOAc/aqueous (1N HCl, water, NaHCO3, and brine) partitions, with purification by trituration with hexane/EtOAc/CH2Cl2 7:3:1 to give the benzyl protected product which was hydrogenated to give 3-((4'-fluorobiphenyl-4-sulfonyl)-(1-hydroxycarbamoylcyclopentyl)amino)pro pionic acid, methyl ester (Ib).

L51 ANSWER 12 OF 85 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN

ACCESSION NUMBER: 2000-170753 [15] WPIX

DOC. NO. CPI: C2000-052983

TITLE: New substituted aryl hydroxamic acids used for treatment of fever, cardiovascular effects, hemorrhage, coagulation, cachexia, anorexia.

DERWENT CLASS: B05

INVENTOR(S): DECICCO, C P; WEXLER, R R; XUE, C

PATENT ASSIGNEE(S): (DUPO) DU PONT PHARM CO; (DUPO) DUPONT PHARM CO

COUNTRY COUNT: 45

PATENT INFORMATION:

PATENT NO	KIND DATE	WEEK	LA	PG	MAIN IPC
<hr/>					
WO 9958528	A1 19991118 (200015)*	EN	70	C07D405-12	
RW: AT BE CH CY DE DK EA ES FI FR GB GR IE IT LU MC NL PT SE					
W: AU BR CA CN CZ EE HU IL IN JP KR LT LV MX NO NZ PL RO SG SI SK UA VN ZA					
AU 9940747	A 19991129 (200018)			C07D405-12	
EP 1077974	A1 20010228 (200113)	EN		C07D405-12	
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LT LU LV NL PT RO SE SI					
US 6268379	B1 20010731 (200146)			C07D217-00	
JP 2002514644	W 20020521 (200236)		74	C07D401-12	

## APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9958528	A1	WO 1999-US10358	19990512
AU 9940747	A	AU 1999-40747	19990512
EP 1077974	A1	EP 1999-924184	19990512
		WO 1999-US10358	19990512
US 6268379	B1 Provisional	US 1998-85393P	19980514
		US 1999-311168	19990513
JP 2002514644	W	WO 1999-US10358	19990512
		JP 2000-548332	19990512

## FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 9940747	A Based on	WO 9958528
EP 1077974	A1 Based on	WO 9958528
JP 2002514644	W Based on	WO 9958528

PRIORITY APPLN. INFO: US 1998-85393P 19980514; US  
1999-311168 19990513

## INT. PATENT CLASSIF.:

MAIN: C07D217-00; C07D401-12; C07D405-12  
 SECONDARY: A61K031-35; A61K031-44; A61K031-4433; A61K031-445;  
 A61K031-4545; A61K031-47; A61K031-4709; A61K031-4725;  
 A61K031-506; A61P001-02; A61P007-02; A61P007-04;  
 A61P009-00; A61P009-02; A61P009-04; A61P009-10;  
 A61P011-00; A61P011-06; A61P019-02; A61P025-00;  
 A61P027-02; A61P029-00; A61P031-00; A61P031-04;  
 A61P031-06; A61P031-08; A61P031-18; A61P033-06;  
 A61P035-00; A61P035-04; A61P037-06; A61P043-00;  
 C07D213-02; C07D401-14; C07D471-04

## BASIC ABSTRACT:

WO 9958528 A UPAB: 20000323

NOVELTY - Substituted **hydroxamic acid** compounds (I) and (II) are new.

DETAILED DESCRIPTION - Substituted **hydroxamic acid** compounds of formulae (I) and (II) are new.

ring A = 5-8 membered cyclic system containing 0-2 heteroatoms chosen from O, NH, S, SO or SO<sub>2</sub> and substituted with 0-3 Ra;

Ra = O, CH<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub>, CF<sub>3</sub>, Cl, F, OH, OCH<sub>3</sub> or OCF<sub>3</sub>;

Rb = F or CH<sub>3</sub>;

X = CH<sub>2</sub>C(O), CH<sub>2</sub>C(O)O, CH<sub>2</sub>C(O)NH, CH<sub>2</sub>S(O), CH<sub>2</sub>S(O)<sub>2</sub>, CH<sub>2</sub>S(O)NH or CH<sub>2</sub>S(O)2NH;

Y = OCH<sub>2</sub>, CH<sub>2</sub>O, OCH(CH<sub>3</sub>), CH(CH<sub>3</sub>)O, OC(CH<sub>3</sub>)<sub>2</sub>, C(CH<sub>3</sub>)<sub>2</sub>O, OCF<sub>2</sub>, CF<sub>2</sub>O,  
S(O)pCH<sub>2</sub>, CH<sub>2</sub>S(O)p, NHCH<sub>2</sub> or CH<sub>2</sub>NH;

Z = CH or N;

R<sub>1</sub> = H, F, Cl, Br, CH<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub>, CH(CH<sub>3</sub>)<sub>2</sub>, OCH<sub>3</sub>, OCH<sub>2</sub>CH<sub>3</sub>, OCH(CH<sub>3</sub>)<sub>2</sub>,  
CF<sub>3</sub> or OCF<sub>3</sub>;

R<sub>2</sub> = F, Cl, Br, I, CH<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub>, CH(CH<sub>3</sub>)<sub>2</sub>, OCH<sub>3</sub>, OCH<sub>2</sub>CH<sub>3</sub>, OCH(CH<sub>3</sub>)<sub>2</sub>,  
CF<sub>3</sub> or OCF<sub>3</sub>;

R<sub>3</sub> = F, Cl, Br, I, CH<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub>, CH(CH<sub>3</sub>)<sub>2</sub>, OCH<sub>3</sub>, OCH<sub>2</sub>CH<sub>3</sub>, OCH(CH<sub>3</sub>)<sub>2</sub>,  
CF<sub>3</sub> or OCF<sub>3</sub>;

R<sub>4</sub> = H;

p = 0-2;

Y' = CH<sub>2</sub>, O or NH.

When Z = N, then R<sub>2</sub> and R<sub>3</sub> are = F, Br or I. Alternately, R<sub>3</sub> and R<sub>4</sub> form 5-6 membered aromatic ring containing 0-2 heteroatoms chosen from O,

S, NH, and N, and the aromatic ring is substituted with 0-2 R<sub>c</sub>.  
 R<sub>c</sub> = H, F, Cl, Br, I, NO<sub>2</sub>, CH<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub>, CH(CH<sub>3</sub>)<sub>2</sub>, OCH<sub>3</sub>, OCH<sub>2</sub>CH<sub>3</sub>, OCH(CH<sub>3</sub>)<sub>2</sub>, CF<sub>3</sub> or OCF<sub>3</sub>.

ACTIVITY - Anti-inflammatory; Antiarthritic.

MECHANISM OF ACTION - Inhibits matrix

metalloproteinase (MMP) and tumor  
necrosis factor (TNF).

USE - Used for treatment of fever, cardiovascular diseases, hemorrhage, coagulation, cachexia, anorexia, alcoholism, acute phase response, acute infection, shock, graft versus host reaction, solid tumor growth and tumor invasion by secondary metastases, or neovascular glaucoma, rheumatoid, arthritis, osteoarthritis, periodontitis, gingivitis, corneal ulceration, multiple sclerosis, neurodegenerative, diseases, psoriasis, autoimmune disease, Crohn's disease, inflammatory bowel disease, or HIV infection (all claimed).

Dwg.0/0

FILE SEGMENT: CPI

FIELD AVAILABILITY: AB; GI; DCN

MANUAL CODES: CPI: B14-C09; B14-D07C; B14-E10; B14-G01B; B14-G02D;  
B14-J01B3; B14-N03; B14-N06B; B14-N17C; B14-S01

TECH UPTX: 20000323

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: (Disclosed) The lactone derivatives of piperidine, 3,4,5,6-tetrahydro-2(1H)-pyrimidinone and tetrahydropyran are converted into a phenylether intermediate, which is then converted into hydroxamic acid by coupling with hydroxylamine hydrochloride using BOP. Oxidation using oxone produces the desired sulfone.

ABEX UPTX: 20000323

SPECIFIC COMPOUNDS - The compound (I) is chosen from 19 claimed compounds, one of them is tetrahydro-N-hydroxy-4-(((4-(4-quinolinylmethoxy)phenyl) sulfonyl)methyl)-2H-pyran-4-carboxamide, which is represented by formula (IV).

ADMINISTRATION - Oral; Topical; Intranasal, Transdermal; Daily oral dosage ranges between 0.001-1000 mg/kg body weight, most preferably 1-20 mg/kg/day.

EXAMPLE - To a cooled solution of 4-mercaptophenol (1.33g, 10.6 mmol) in THF (30 mL) was added NaH (0.98g, 24.6 mmol). Mixture was allowed to warm to room temperature, and added with a solution of 2,7-dioxaspiro(3,5)nonane-1-one (1.0 g, 7 mmol) in THF (5 mL). The mixture was stirred, quenched with 1 N HCl, and extracted with ethyl acetate followed by washing the organic layers with carboxylic acid. The solution of the acid (1a) (700 mg, 2.6 mmol) and 4-dimethylaminopyridine (63 mg, 0.5 mmol) in methylene chloride (5 mL) and methanol (1 mL) was added with 1,3-dicyclohexylcarbodiimide (640 mg, 3.1 mmol). The mixture was filtered, concentrated and chromatographically eluted to obtain methyl ester. The methyl ester (300 mg), 2,6-dimethyl-4-picolyll chloride (213 mg), cesium carbonate (1.03 g), and tetrabutylammonium iodide (392 mg) in DMSO (3mL) were heated at 50 degreesC. Ethyl acetate was added and the solution was washed, dried, concentrated and chromatographed on a reversed HPLC to give the phenylether as a TFA salt. The phenylether (200 mg) in methanol (5 mL) and 1 N LiOH (4mL) was refluxed for 5 hours. The solution was acidified with 1 N HCl and concentrated. The crude acid (0.388 mmol), hydroxylamine hydrochloride (139 mg, 2 mmol) and diisopropylethylamine (0.7 mL, 4 mmol) in DMF (3 mL) were cooled in an ice bath and BOP (220 mg, 0.5 mmol) was added. The mixture was stirred at room temperature for 2 hours and concentrated. Purification on HPLC gave the hydroxamic acid. A solution of cooled the phenylether (95 mg) in methanol (3 mL) cooled in an ice bath was added a solution of oxone (0.28 g) in water (1 mL). The

mixture was stirred at room temperature for 4 hours and insoluble material was filtered off and the solution was concentrated. On purification using reversed high performance liquid chromatography (HPLC), (11 mg) of 4-(((4-(2,6-dimethyl-4-pyridinyl)methoxy)phenyl)sulfonyl)methyl)tetrahydro-N-hydroxy-2H-pyran-4-carboxamide mono(trifluoroacetate) was obtained.

**DEFINITIONS - Preferred Definitions:**

X = CH<sub>2</sub>, C(O), C(O)O, C(O)NH, S(O), S(O)<sub>2</sub>, S(O)NH or S(O)2NH;  
Y = (CH<sub>2</sub>)<sub>2</sub>, OCH<sub>2</sub>, CH<sub>2</sub>O, NHCH<sub>2</sub> or CH<sub>2</sub>NH;  
Y' = CH<sub>2</sub>, O, S or NH;  
R<sub>3</sub> and R<sub>4</sub> = (optionally) is one of 27 claimed aromatic rings, e.g.  
formula (III);  
R<sub>2a</sub> = H, F, Cl, Br, I, CH<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub>, CH(CH<sub>3</sub>)<sub>2</sub>, OCH<sub>3</sub>, OCH<sub>2</sub>CH<sub>3</sub>, OCH(CH<sub>3</sub>)<sub>2</sub>, CF<sub>3</sub> or OCF<sub>3</sub>;  
R<sub>c</sub> = H, F, Cl, Br, I, NO<sub>2</sub>, CH<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub>, CH(CH<sub>3</sub>)<sub>2</sub>, OCH<sub>3</sub>, OCH<sub>2</sub>CH<sub>3</sub>, OCH(CH<sub>3</sub>)<sub>2</sub>, CF<sub>3</sub> or OCF<sub>3</sub>.

L51 ANSWER 13 OF 85 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN  
ACCESSION NUMBER: 1998-312004 [27] WPIX  
DOC. NO. CPI: C1998-096182  
TITLE: New ortho-sulphonamide hetero-aryl hydroxamic acid derivatives - are matrix metallo-proteinase and tumour necrosis alpha converting enzyme inhibitors used for treating arthritis and tumour growth, etc..  
DERWENT CLASS: B05 D21  
INVENTOR(S): ALBRIGHT, J D; DUI, X; GU, Y; LEVIN, J I; ZASK, A; DU, X  
PATENT ASSIGNEE(S): (AMCY) AMERICAN CYANAMID CO  
COUNTRY COUNT: 77  
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN	IPC
<hr/>							
WO 9816514	A1	19980423 (199827)*	EN	57	C07D215-54		
RW: AT BE CH DE DK ES FI FR GB GH GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW							
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH HU IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZW							
AU 9749806	A	19980511 (199837)			C07D215-54		
ZA 9709235	A	19990630 (199931)		57	C07D000-00		
AU 743901	B	20020207 (200224)			C07D215-54		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
<hr/>			
WO 9816514	A1	WO 1997-US18281	19971008
AU 9749806	A	AU 1997-49806	19971008
ZA 9709235	A	ZA 1997-9235	19971015
AU 743901	B	AU 1997-49806	19971008

FILING DETAILS:

PATENT NO	KIND	PATENT NO
<hr/>		
AU 9749806	A Based on	WO 9816514
AU 743901	B Previous Publ.	AU 9749806

Based on

WO 9816514

PRIORITY APPLN. INFO: US 1996-732004 19961016

INT. PATENT CLASSIF.:

MAIN: C07D000-00; C07D215-54  
 SECONDARY: A61K031-47; C07D401-12; C07D409-12; C07D409-14;  
 C07D471-04; C07F000-00

## BASIC ABSTRACT:

WO 9816514 A UPAB: 19980709

Ortho-sulphonamide bicyclic heteroaryl **hydroxamic acid** derivatives of formula (I) and their salts and optical isomers or diastereoisomers are new. A = 5-6 membered heteroaryl containing 1-2 heteroatoms comprising N, O and/or S (substituted by R1 and R2 on adjacent atoms); CR1CR2 = a fused Ph or 5-6 membered heteroaryl containing 1-3 heteroatoms comprising N, O and/or S (either ring optionally substituted by R4); **hydroxamic acid** and sulphonamido groups are bonded to adjacent C atoms of heteroaryl ring of A; Z = aryl, heteroaryl or heteroaryl fused to Ph; aryl = Ph or naphthyl (optionally substituted by R1-R4); heteroaryl = 5-6 membered heteroaromatic ring containing 1-3 heteroatoms comprising N, O and/or S (optionally substituted by R1-R4), provided that when heteroaryl is fused to Ph, at least 1 ring is optionally substituted by R1-R4; R1-R4 = H, COR5, F, Br, Cl, I, C(O)NR5OR6, CN, OR5, 1-4C perfluoroalkyl, SOxR5, OPO(OR5)(OR6), PO(OR6)R5, OC(O)NR5R6, CO2R5, CONR5R6, SO3H, NR5R6, NR5COR6, NR5COOR6, SO2NR5R6, NO2, N(R5)SO2R6, NR5CONR5R6, NR5C(=NR6)NR5R6, cychet, aryl, heteroaryl, SO2NHCOR5', CONHSO2R5', tetrazol-5-yl, SO2NHCN, SO2NHCONR5R6, 1-6C alkyl, 2-6C alkenyl or 2-6C alkynyl or 3-6C cycloalkyl (optionally having 1-2 double bonds (each optionally substituted by Q)); Q = COR5, CN, 2-6C alkenyl, 2-6C alkynyl, OR5, 1-4C perfluoroalkyl, SOxR5, OC(O)NR5R6, CO2R5, CONR5R6, SO3H, NR5R6, NR5COR6, NR5CO2R6, SO2NR5R6, NO2, N(R5)SO2R6, NR5CONR5R6, 3-6C cycloalkyl (optionally having 1-2 double bonds (each optionally substituted by Q)), cychet, aryl, heteroaryl, SO2NHCOR5', CONHSO2R5', PO(OR5)OR6, PO(OR6)R5, tetrazol-5-yl, C(O)NR5OR6, NR5C(=NR6)NR5R6, SO2NHCONR5R6 or SO2NHCN; x = 0-2; cychet = 3-6 membered cycloheteroalkyl (containing 1-3 heteroatoms comprising O, N and/or S and optionally having 1-2 double bonds and optionally substituted by 1-3 R5); R5, R6 = H, aryl, heteroaryl, 3-6C cycloalkyl (optionally having 1-2 double bonds (each optionally substituted by Q)), cychet, 1-4C perfluoroalkyl or 1-6C alkyl, 2-6C alkenyl or 2-6C alkynyl (all optionally substituted by OH, COR8, CN, C(O)NR8OR9, 2-6C alkenyl, 2-6C alkynyl, OR8, 1-4C perfluoroalkyl, SOxR8, OPO(OR8)OR9, PO(OR8)R9, OC(O)NR8R9, CO2R8, CONR8R9, SO3H, NR8R9, NHCOR8R9, NR8CO2R9, SO2NR8R9, NO2, NR8SO2R9, NR8CONR8R9, 3-6C cycloalkyl (optionally having 1-2 double bonds (each optionally substituted by Q)), cychet, aryl, heteroaryl, SO2NHCOR8', CONHSO2R8', tetrazol-5-yl, NR8C(=NR9)NR8R9, SO2NHCONR8R9 or SO2NHCN); R5' = a group R5 excluding H; R7 = (a) H or 1-6C alkyl, 2-6C alkenyl or 2-6C alkynyl (all optionally substituted by OH, COR5, CN, 2-6C alkenyl, 2-6C alkynyl, OR5, 1-4C perfluoroalkyl, SOxR5, OPO(OR5)OR6, PO(OR5)R6, OC(O)NR5R6, COOR5, CONR5R6, SO3H, NR5R6, NR5COR6, NR5COOR6, SO2NR5R6, NO2, N(R5)SO2R6, NR5CONR5R6, 3-6C cycloalkyl, cychet, aryl, heteroaryl, SO2NHCOR5', CONHSO2R5', tetrazol-5-yl, NR5C(=NR6)NR5R6, CONR5OR6, SO2NHCONR5R6 or SO2NHCN; (b) Ph or naphthyl (optionally substituted by R1-R4) or 5-6 membered heteroaryl containing 1-3 heteroatoms comprising N, O and/or S and optionally substituted by R1-R4 or (c) 3-6C cycloalkyl (optionally having 1-2 double bonds (each optionally substituted by Q)) or cychet or R7CH2NA = a non-aromatic 7-12 membered heterocycle optionally containing an additional heteroatom selected from O, S and N and optionally fused to another benzene ring; R8, R9 = H, aryl, heteroaryl, 3-7C cycloalkyl (optionally having 1-2 double bonds (each optionally substituted by Q)), cychet, 1-4C perfluoroalkyl, 1-6C alkyl, 2-6C alkenyl

or 2-6C alkynyl (all optionally substituted by OH, alkoxy, aryloxy, 1-4C perfluoroalkyl, amino, mono- or di-(1-6C alkyl)amino, carboxylic acid, carboalkoxy or carboaryloxy), NO<sub>2</sub>, CN, carboxamido primary, mono- or di-(1-6C alkyl)carbamoyl; R8' = a group R8 excluding H. N.B. Some of the groups are cyclical.

52 Compounds are specifically claimed eg: 4-(benzyl-(4-methoxybenzenesulphonyl)amino)-7-trifluoromethyl-quinoline-3-carboxylic acid hydroxyamide.

USE - (I) are matrix metalloproteinase (MMP) and tumour necrosis factor alpha converting enzyme inhibitors used to inhibit e.g. gelatinases, stromelysins and collagenases. (I) are useful for treating atherosclerosis, atherosclerotic plaque formation, reduction of coronary thrombosis from atherosclerotic plaque rupture, MMP mediated osteopenias, inflammatory of the central nervous system, skin ageing, angiogenesis, tumour metastasis, tumour growth, osteoarthritis, rheumatoid arthritis, septic arthritis, corneal ulceration, abnormal wound healing, bone disease, proteinuria, aneurysmal aortic disease, degenerative cartilage loss following traumatic joint injury, demyelinating diseases of the nervous system, cirrhosis of the liver, glomerular disease of the kidney, premature rupture of foetal membranes, inflammatory bowel disease, periodontal disease, age related macular degeneration, diabetic retinopathy, proliferative vitreoretinopathy, retinopathy of prematurity, ocular inflammation, ketatoconus, Sjogren's syndrome, myopia, ocular tumours, ocular angiogenesis and neovascularisation, corneal graft rejection, graft rejection, cachexia, anorexia, inflammation, fever, insulin resistance, septic shock, congestive heart failure and HIV infection.

Dwg.0/0

FILE SEGMENT: CPI  
 FIELD AVAILABILITY: AB; GI; DCN  
 MANUAL CODES: CPI: B06-D02; B07-D04C; B07-D08; B14-A02B1; B14-C03;  
                   B14-C09; B14-D07C; B14-E10; B14-F01B; B14-F02;  
                   B14-G02D; B14-H01; B14-J01; B14-N03; B14-N10;  
                   B14-N12; B14-N17B; D08-A05; D08-B09A

L51 ANSWER 14 OF 85 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN  
 ACCESSION NUMBER: 1996-425356 [42] WPIX

DOC. NO. CPI: C1996-134034

TITLE: New aryl-sulphonyl-amino hydroxamic acid  
 derivs. - are matrix metallo-  
 proteinase inhibitors and  
 inhibitors of production of tumour  
 necrosis factor, used for treating arthritis and  
 cancer, etc..

DERWENT CLASS: B03 B05 D21

INVENTOR(S): RIZZI, J P; ROBINSON, R P

PATENT ASSIGNEE(S): (PFIZ) PFIZER INC; (PFIZ) PFIZER CORP

COUNTRY COUNT: 74

PATENT INFORMATION:

PATENT NO	KIND DATE	WEEK	LA	PG	MAIN IPC
WO 9627583	A1 19960912 (199642)* EN	70	C07C311-29		
RW: AT BE CH DE DK EA ES FI FR GB GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG					
W: AL AM AT AU AZ BB BG BR BY CA CH CN CZ DE DK EE ES FI GB GE HU IS JP KE KG KP KR KZ LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG US UZ VN					
AU 9650293	A 19960923 (199702)			C07C311-29	

ZA 9601876	A	19971126 (199802)	56 C07C000-00
NO 9704103	A	19971105 (199804)	C07C311-29
EP 813520	A1	19971229 (199805) EN	C07C311-29
R: AT BE CH DE DK ES FR GB GR IE IT LI LU NL PT SE			
FI 9703613	A	19971105 (199806)	C07C000-00
BR 9607362	A	19971230 (199807)	C07C311-29
NZ 303860	A	19980826 (199840)	C07C311-29
HU 9800462	A2	19980728 (199842)	C07C311-29
CZ 9702782	A3	19981111 (199851)	C07C311-29
MX 9706850	A1	19971101 (199902)	C07C311-29
US 5863949	A	19990126 (199911)	A61K031-185
JP 11501910	W	19990216 (199917)	71 C07C311-29
TW 346488	A	19981201 (199919)	C07D265-30
KR 98702820	A	19980805 (199932)	C07C311-29
AU 707510	B	19990715 (199939)	C07C311-29
US 5994351	A	19991130 (200003)	A61K031-495
RU 2145597	C1	20000220 (200048)	C07C311-29
US 6147074	A	20001114 (200060)	A61K031-192
KR 269046	B1	20001016 (200138)	C07C311-29
EP 813520	B1	20011219 (200206) EN	C07C311-29
R: AT BE CH DE DK ES FR GB GR IE IT LI LU NL PT SE			
CN 1316419	A	20011010 (200207)	C07C311-29
DE 69618179	E	20020131 (200216)	C07C311-29
US 6380219	B1	20020430 (200235)	A61K031-4468
CN 1181066	A	19980506 (200236)	C07C311-29
ES 2169794	T3	20020716 (200256)	C07C311-29
IL 117343	A	20020814 (200272)	C07C311-19
NO 313752	B1	20021125 (200302)	C07C311-29
CZ 291106	B6	20021211 (200309)	C07C311-29
MX 208185	B	20020605 (200366)	A61K031-18
CA 2214720	C	20040127 (200412) EN	A61K031-535
CN 1122662	C	20031001 (200553)	C07C311-29

## APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9627583	A1	WO 1996-US2679	19960307
AU 9650293	A	AU 1996-50293	19960307
ZA 9601876	A	ZA 1996-1876	19960307
NO 9704103	A	WO 1996-US2679 NO 1997-4103	19960307 19970905
EP 813520	A1	EP 1996-907134 WO 1996-US2679	19960307 19960307
FI 9703613	A	WO 1996-US2679 FI 1997-3613	19960307 19970905
BR 9607362	A	BR 1996-7362 WO 1996-US2679	19960307 19960307
NZ 303860	A	NZ 1996-303860 WO 1996-US2679	19960307 19960307
HU 9800462	A2	WO 1996-US2679 HU 1998-462	19960307 19960307
CZ 9702782	A3	WO 1996-US2679 CZ 1997-2782	19960307 19960307
MX 9706850	A1	MX 1997-6850	19970908
US 5863949	A	WO 1996-US2679 US 1997-894873	19960307 19970804
JP 11501910	W	JP 1996-526918 WO 1996-US2679	19960307 19960307
TW 346488	A	TW 1996-104697	19960419

KR 98702820	A	WO 1996-US2679	19960307
		KR 1997-706227	19970906
AU 707510	B	AU 1996-50293	19960307
US 5994351	A Div ex	WO 1996-US2679	19960307
	Div ex	US 1997-894873	19970804
		US 1998-122920	19980727
RU 2145597	C1	WO 1996-US2679	19960307
		RU 1997-116727	19960307
US 6147074	A Div ex	WO 1996-US2679	19960307
	Div ex	US 1997-894873	19970804
	Div ex	US 1998-122920	19980727
		US 1999-406522	19990928
KR 269046	B1	WO 1996-US2679	19960307
		KR 1997-706227	19970906
EP 813520	B1	EP 1996-907134	19960307
		WO 1996-US2679	19960307
CN 1316419	A	CN 2001-111743	20010323
DE 69618179	E	DE 1996-618179	19960307
		EP 1996-907134	19960307
		WO 1996-US2679	19960307
US 6380219	B1 Div ex	US 1997-894873	19970804
	Div ex	US 1998-122920	19980727
	Div ex	US 1999-406522	19990928
		US 2000-635186	20000808
CN 1181066	A	CN 1996-193213	19960307
ES 2169794	T3	EP 1996-907134	19960307
IL 117343	A	IL 1996-117343	19960304
NO 313752	B1	WO 1996-US2679	19960307
		NO 1997-4103	19970905
CZ 291106	B6	WO 1996-US2679	19960307
		CZ 1997-2782	19960307
MX 208185	B	WO 1996-US2679	19960307
		MX 1997-6850	19970908
CA 2214720	C	CA 1996-2214720	19960307
		WO 1996-US2679	19960307
CN 1122662	C	CN 1996-193213	19960307

## FILING DETAILS:

PATENT NO	KIND	PATENT NO
-----	-----	-----
AU 9650293	A Based on	WO 9627583
EP 813520	A1 Based on	WO 9627583
BR 9607362	A Based on	WO 9627583
NZ 303860	A Based on	WO 9627583
HU 9800462	A2 Based on	WO 9627583
CZ 9702782	A3 Based on	WO 9627583
US 5863949	A Based on	WO 9627583
JP 11501910	W Based on	WO 9627583
KR 98702820	A Based on	WO 9627583
AU 707510	B Previous Publ.	AU 9650293
	Based on	WO 9627583
US 5994351	A Div ex	US 5863949
RU 2145597	C1 Based on	WO 9627583
US 6147074	A Div ex	US 5994351
EP 813520	B1 Based on	WO 9627583
DE 69618179	E Based on	EP 813520
	Based on	WO 9627583
US 6380219	B1 Div ex	US 5863949
	Div ex	US 5994351

	Div ex	US 6147074
ES 2169794	T3 Based on	EP 813520
NO 313752	B1 Previous Publ.	NO 9704103
CZ 291106	B6 Previous Publ.	CZ 9702782
	Based on	WO 9627583
CA 2214720	C Based on	WO 9627583

PRIORITY APPLN. INFO: US 1995-401049                    19950308; US  
                               1997-894873                    19970804; US  
                               1998-122920                    19980727; US  
                               1999-406522                    19990928; US  
                               2000-635186                    20000808

REFERENCE PATENTS: EP 606046; WO 9005719

INT. PATENT CLASSIF.:

MAIN:	A61K031-18; A61K031-185; A61K031-192; A61K031-4468; A61K031-495; A61K031-535; C07C000-00; C07C311-19; C07C311-29; C07D265-30; C07D295-185
SECONDARY:	A61K031-195; A61K031-215; A61K031-335; A61K031-38; A61K031-395; A61K031-40; A61K031-44; A61K031-445; A61K031-47; A61K031-5375; A61K031-54; A61P001-04; A61P019-02; A61P029-00; A61P031-02; A61P031-18; A61P035-00; A61P037-00; A61P043-00; C07C303-40; C07C311-18; C07C317-26; C07C323-23; C07C323-50; C07D207-12; C07D207-335; C07D209-08; C07D209-44; C07D211-06; C07D211-26; C07D211-56; C07D211-60; C07D211-66; C07D213-40; C07D213-56; C07D213-75; C07D215-08; C07D217-06; C07D241-04; C07D241-08; C07D295-12; C07D295-15; C07D295-18; C07D295-19; C07D295-192; C07D309-08; C07D309-14; C07D335-02; C07D401-02; C07D403-02; C07D405-02; C07D409-02; C07D413-02; C07D413-12; C07D417-02; C07D471-08; C07D473-00; C07D487-08

BASIC ABSTRACT:

WO 9627583 A UPAB: 19981021  
 Arylsulphonylamino hydroxamic acid derivs. of formula (I) and their salts are new. n = 1-6; X = OH, 1-6 C alkoxy or NR1R2; R1, R2 = e.g. H, 1-6 C alkyl, piperidyl, 1-6 C alkyl-piperidyl, 6-10 C aryl-piperidyl, 5-9 C heteroaryl-piperidyl, 6-10 C aryl, 1-6 C alkyl-piperidyl, R5(2-6 C alkyl), 1-5 C alkyl (CHR5)-1-6 C alkyl, R6(1-6 C alkyl), 1-56 C alkyl (CHR6)-1-6 C alkyl or CH(R7)COR8, etc.; R5 = e.g. OH, 1-6 C acyloxy, 1-6 C alkoxy, piperazino, 1-6 C acylamino, 1-6 C alkylthio, 6-10 C arylthio, 1-6 C alkyl-sulphanyl, etc.; R6 = piperidyl, 1-6 C alkyl-piperidyl, 6-10 C aryl-piperidyl, 6-10 C aryl-1-6 C alkyl-piperidyl, 5-9 C heteroaryl-piperidyl or 5-9 C heteroaryl-1-6 C alkyl-piperidyl; R7 = e.g. H, 1-6 C alkyl 6-10 C aryl-1-6 C alkyl, 5-9 C heteroaryl-1-6 C alkyl, 1-6 C alkylthio-1-6 C alkyl, 6-10 C arylthio-1-6 C alkyl, 1-6 C alkylsulphanyl-1-6 C alkyl, 6-10 C arylsulphanyl-1-6 C alkyl, or 1-6 C alkyl-sulphonyl-1-6 C alkyl, R9R10NCO-1-6 C alkyl or R9OCO-1-6 C alkyl, etc.; R8 = R11O or R11R12N; R9-R12 = H, 1-6 C alkyl, 6-10 C aryl-1-6 C alkyl or 5-9 C heteroaryl-1-6 C alkyl; or R1, R2, or R9 and R10, or R11 and R12 may be taken together to form an azetidinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, indolinyl, isoindolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, 1-6 C acyl-piperazinyl, 1-6 C alkyl-piperazinyl, 6-10 C aryl-piperazinyl, 5-9 C heteroaryl-piperazinyl or a bridged diazabicycloalkyl ring selected from (a)-(e); r = 1-3; m = 1-2; p = 0-1; Q = H, 1-3 C alkyl or 1-6 C acyl; R3, R4 = e.g. H, 1-6 C alkyl, CF<sub>3</sub>, trifluoromethyl-1-6 C alkyl, 1-6 C alkyl (difluoromethylene), 1-3 C alkyl(difluoromethylene)- 1-3 C alkyl, 6-10 C aryl, 5-9 C heteroaryl, 6-10 C aryl-1-6 C alkyl, 1-6 C alkylsulphonyl-1-6 C alkyl, 6-10 C arylsulphonyl-1-6 C alkyl, amino-1-6 C alkyl, 1-6 C

alkylamino-1-6 C alkyl, (1-6 C alkylamino)2-1-6 C alkyl, R13CO -1-6 C alkyl or R14-1-6 C alkyl, etc.; R13 = R20O or R20R21N; R20, R21 = H, 1-6 C alkyl, 6-10 C aryl-1-6 C alkyl or 5-9 C heteroaryl-1-6 C alkyl; R14 = 1-6 C acyl-piperazino, 6-10 C aryl-piperazino, 5-9 C heteroaryl-piperazino, 1-6 C alkyl-piperazino, 6-10 C aryl-1-6 C alkyl-piperazino, 5-9 C heteroaryl- 1-6 C alkyl-piperazino, morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl, 1-6 C alkyl-piperidyl, 6-10 C aryl-piperidyl, 5-9 C heteroaryl-piperidyl, 6-10 C aryl-1-6 C alkyl-piperidyl, 5-9 C heteroaryl-1-6 C alkylpiperidyl or 1-6 C acyl-piperidyl; or R3 and R4, or R20 and R21 may be taken together to form a 3-6 C cycloalkyl, oxacyclohexyl, thiocyclohexyl, indanyl or tetralinyl ring or a gp. of formula (f): R15 = H, 1-6 C acyl, 1-6 C alkyl, 6-10 C aryl-1-6 C alkyl, 5-9 C heteroaryl-1-6 C alkyl or 1-6 C alkylsulphonyl; Ar = 6-10 C aryl, 5-9 C heteroaryl, 1-6 C alkyl-6-10 C aryl, 1-6 C alkoxy-6-10 C aryl, (1-6 C alkoxy)2- 6-10 C aryl, 6-10 C aryloxy-6-10 C aryl, 5-9 C heteroaryloxy-6-10 C aryl, 1-6 C alkyl-5-9 C heteroaryl, 1-6 C alkoxy-5-9 C heteroaryl, (1-6 C alkoxy)2-5-9 C heteroaryl, 6-10 C aryloxy-5-9 C heteroaryl or 5-9 C heteroaryloxy-5-9 C heteroaryl; with the proviso that when either R1 or R2 is CH(R7) COR8, the other of R1 and R2 is H, 1-6 C alkyl or benzyl.

USE - (I) can be used to inhibit matrix metalloproteinases (MMPs) or to inhibit the production of tumour necrosis factor (TNF) in a mammal (claimed). (I) can be used to treat arthritis, cancer, tissue ulceration, restenosis, periodontal disease, epidermolysis bullosa, scleritis and other diseases characterised by MMP activity (claimed). (I) can also be used to treat AIDS, sepsis, septic shock and other diseases involving the production of TNF (claimed). (I) can be used in doses of e.g. 0.1-25, pref. 0.3-5 mg/kg/day by e.g. oral, parenteral or topical routes.

Dwg.0/0

FILE SEGMENT: CPI  
 FIELD AVAILABILITY: AB; GI; DCN  
 MANUAL CODES: CPI: B06-H; B07-H; B10-A08; B14-A02B1; B14-C09; B14-D07C; B14-F01E; B14-H01; B14-L06; B14-N06; B14-S06; D08-A05

=> d ibib ed ab hitind 15-

YOU HAVE REQUESTED DATA FROM FILE 'WPIX, MEDLINE, EMBASE, BIOSIS, PASCAL, CANCERLIT, DRUGU, SCISEARCH' - CONTINUE? (Y)/N:y

YOU HAVE REQUESTED DATA FROM 71 ANSWERS - CONTINUE? Y/(N):y

L51	ANSWER 15 OF 85	MEDLINE on STN	DUPPLICATE 2
ACCESSION NUMBER:	2003601428	MEDLINE	
DOCUMENT NUMBER:	PubMed ID: 14684295		
TITLE:	Tetrahydroisoquinoline based sulfonamide hydroxamates as potent matrix metalloproteinase inhibitors.		
AUTHOR:	Ma Dawei; Wu Wengen; Yang Guoxin; Li Jingya; Li Jia; Ye Qizhuang		
CORPORATE SOURCE:	State Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China.. madw@mail.sioc.ac.cn		
SOURCE:	Bioorganic & medicinal chemistry letters, (2004 Jan 5) 14(1) 47-50. Journal code: 9107377. ISSN: 0960-894X.		

PUB. COUNTRY: England: United Kingdom  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200408  
 ENTRY DATE: Entered STN: 20031220  
               Last Updated on STN: 20040828  
               Entered Medline: 20040827

ED   Entered STN: 20031220  
      Last Updated on STN: 20040828  
      Entered Medline: 20040827

AB   The synthesis and MMP inhibitory activity of a series of tetrahydroisoquinoline based sulfonamide hydroxamates are described. In nine MMPs tested, most of the compounds display potent inhibition activity except for MMP-7. Some subtle isozyme selectivity is observed by varying the substituents at the 6- and 7-positions and aromatic ring of arylsulfonyl groups.

CT   \*Enzyme Inhibitors: CH, chemistry  
      Enzyme Inhibitors: PD, pharmacology  
      \*Hydroxamic Acids: CH, chemistry  
       Hydroxamic Acids: PD, pharmacology  
      \*Matrix Metalloproteinases: AI, antagonists & inhibitors  
       Matrix Metalloproteinases: ME, metabolism  
       Research Support, Non-U.S. Gov't  
      \*Sulfonamides: CH, chemistry  
       Sulfonamides: PD, pharmacology  
      \*Tetrahydroisoquinolines: CH, chemistry  
       Tetrahydroisoquinolines: PD, pharmacology

CN   0 (Enzyme Inhibitors); 0 (Hydroxamic Acids); 0 (Sulfonamides); 0 (Tetrahydroisoquinolines); EC 3.4.24.- (Matrix Metalloproteinases)

L51 ANSWER 16 OF 85           MEDLINE on STN                   DUPLICATE 3  
 ACCESSION NUMBER: 2002455012       MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 12213468  
 TITLE: Tetrahydroisoquinoline-3-carboxylate based matrix-metalloproteinase inhibitors: design, synthesis and structure-activity relationship.  
 AUTHOR: Matter Hans; Schudok Manfred; Schwab Wilfried; Thorwart Werner; Barbier Denis; Billen Gunter; Haase Burkhard; Neises Bernhard; Weithmann Klaus; Wollmann Theo  
 CORPORATE SOURCE: Aventis Pharma Deutschland GmbH, D-65926 Frankfurt am Main, Germany.. hans.matter@aventis.com  
 SOURCE: Bioorganic & medicinal chemistry, (2002 Nov) 10 (11) 3529-44.  
 Journal code: 9413298. ISSN: 0968-0896.  
 PUB. COUNTRY: England: United Kingdom  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200303  
 ENTRY DATE: Entered STN: 20020906  
              Last Updated on STN: 20030305  
              Entered Medline: 20030304

ED   Entered STN: 20020906  
      Last Updated on STN: 20030305  
      Entered Medline: 20030304

AB   The design, synthesis and structure-activity relationship (SAR) of a series of nonpeptidic 2-arylsulfonyl-1,2,3,4-tetrahydro-isoquinoline-3-carboxylates and-hydroxamates as inhibitors of the matrix metalloproteinase human

neutrophil collagenase (**MMP-8**) is described here. Based on available X-ray structures of **MMP-8/inhibitor** complexes, our structure-based design strategy was directed to complement major protein-ligand interaction regions mainly in the S1' hydrophobic specificity pocket close to the catalytic zinc ion. Here, the rigid 1,2,3,4-tetrahydroisoquinoline scaffold (Tic) provides ideal geometry to combine **hydroxamates** and carboxylates as typical zinc complexing functionalities, with a broad variety of S1' directed mono- and biaryl substituents consisting of aromatic rings perfectly accommodated within this more hydrophobic region of the **MMP-8** inhibitor binding site. The effect of different S1' directed substituents, zinc-complexing groups, chirality and variations of the tetrahydroisoquinoline ring-system is investigated by systematic studies. X-ray structure analyses in combination with 3D-QSAR studies provided an additional understanding of key determinants for **MMP-8** affinity in this series. The hypothetical binding mode for a typical molecule as basis for our inhibitor design was found in good agreement with a 1.7 Å X-ray structure of this candidate in complex with the catalytic domain of human **MMP-8**. After analysis of all systematic variations, 3D-QSAR and X-ray structure analysis, novel S1' directed substituents were designed and synthesized and biologically evaluated. This finally results in inhibitors, which do not only show high biological affinity for **MMP-8**, but also exhibit good oral bioavailability in several animal species.

CT Check Tags: In Vitro  
Animals  
Biological Availability  
Computational Biology  
Crystallography, X-Ray  
Drug Design  
Gelatinase B: AI antagonists & inhibitor

Gelatinase B: AI, antagonists & inhibitors  
Humans  
Indicators and Reagents  
\*Isoquinolines: CS, chemical synthesis  
\*Isoquinolines: PD, pharmacology  
\*Matrix Metalloproteinases: AI, antagonists & inhibitors

- \*Matrix Metalloproteinases: AI, anti-  
Models, Molecular  
Molecular Conformation
- Neutrophils: DE, drug effects  
Neutrophils: EN, enzymology
- \*Protease Inhibitors: CS, chemical synthesis  
Protease Inhibitors: PK, pharmacokinetics
- \*Protease Inhibitors: PD, pharmacology  
Quantitative Structure-Activity Relationship

Rabbits  
\*Tetrahydroisoquinolines  
RN 41034-52-0 (1,2,3,4-tetrahydroisoquinoline carboxylic acid)  
CN 0 (Indicators and Reagents); 0 (Isoquinolines); 0 (Protease Inhibitors); 0  
(Tetrahydroisoquinolines); EC 3.4.24.- (Matrix Metalloproteinases); EC  
3.4.24.35 (Gelatinase B)

L51 ANSWER 17 OF 85 MEDLINE on STN DUPLICATE 4  
ACCESSION NUMBER: 2000048220 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 10579815  
TITLE: Affinity and selectivity of matrix metalloproteinase inhibitors: a chemometrical study from the perspective of ligands and proteins.  
AUTHOR: Matter H; Schwab W  
CORPORATE SOURCE: Hoechst Marion Roussel, Chemical Research, D-65926 Frankfurt am Main, Germany.. hans.matter@hmrag.com

SOURCE: Journal of medicinal chemistry, (1999 Nov 4) 42 (22)  
 4506-23.  
 Journal code: 9716531. ISSN: 0022-2623.

PUB. COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 199912  
 ENTRY DATE: Entered STN: 20000113  
 Last Updated on STN: 20000113  
 Entered Medline: 19991217

ED    Entered STN: 20000113  
 Last Updated on STN: 20000113  
 Entered Medline: 19991217

AB    A novel strategy to understand affinity and selectivity for enzyme inhibitors using information from ligands and target protein 3D structures is described. It was applied to 2-arylsulfonyl-1,2,3, 4-tetrahydro-isoquinoline-3-carboxylates and -hydroxamates as inhibitors of the **matrix metalloproteinases** **MMP-3** (stromelysin-1) and **MMP-8** (human neutrophil collagenase). As the first step, consistent and predictive 3D-QSAR models were derived using CoMFA, CoMSIA, and GRID/Golpe approaches, leading to the identification of binding regions where steric, electronic, or hydrophobic effects are important for affinity. These models were validated using multiple analyses using two or five randomly chosen cross-validation groups and randomizations of biological activities. Second, 3D-QSAR models were derived based on the affinity ratio IC(50) (**MMP-8**)/IC(50) (**MMP-3**), allowing the identification of key ligand determinants for selectivity toward one of both enzymes. In addition to this ligands' view, the third step encompasses a chemometrical approach based on principal component analysis (PCA) of multivariate GRID descriptors to uncover the major differences between both protein binding sites with respect to their GRID probe interaction pattern. The resulting information, based on the accurate knowledge of the target protein 3D structures, led to a consistent picture in good agreement with experimentally observed differences in selectivity toward **MMP-8** or **MMP-3**. The interpretation of all three classes of statistical models leads to detailed SAR information for **MMP** inhibitors, which is in agreement with available data for binding site topologies, ligand affinities, and selectivities. Thus the combined chemical analyses provide guidelines and accurate activity predictions for designing novel, selective **MMP** inhibitors.

CT    Carboxylic Acids: CH, chemistry  
 Hydroxamic Acids: CH, chemistry  
 Isoquinolines: CH, chemistry  
 Ligands  
 Models, Molecular  
 Molecular Structure  
 Neutrophil Collagenase: AI, antagonists & inhibitors  
 \*Neutrophil Collagenase: CH, chemistry  
 \*Protease Inhibitors: CH, chemistry  
 Protein Binding  
 Protein Conformation  
 Stromelysin 1: AI, antagonists & inhibitors  
 \*Stromelysin 1: CH, chemistry  
 Structure-Activity Relationship

CN    0 (Carboxylic Acids); 0 (Hydroxamic Acids); 0 (Isoquinolines); 0 (Ligands); 0 (Protease Inhibitors); EC 3.4.24.17 (Stromelysin 1); EC 3.4.24.34 (Neutrophil Collagenase)

L51 ANSWER 18 OF 85 MEDLINE on STN DUPLICATE 5  
 ACCESSION NUMBER: 1999284661 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 10354399  
 TITLE: Quantitative structure-activity relationship of human neutrophil collagenase (MMP-8) inhibitors using comparative molecular field analysis and X-ray structure analysis.  
 AUTHOR: Matter H; Schwab W; Barbier D; Billen G; Haase B; Neises B; Schudok M; Thorwart W; Schreuder H; Brachvogel V; Lonze P; Weithmann K U  
 CORPORATE SOURCE: Chemical Research & Core Research Functions, Hoechst Marion Roussel, D-65926 Frankfurt am Main, Germany..  
 SOURCE: Journal of medicinal chemistry, (1999 Jun 3) 42 (11) 1908-20.  
 PUB. COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 199906  
 ENTRY DATE: Entered STN: 19990712  
 Last Updated on STN: 20000303  
 Entered Medline: 19990624  
 ED Entered STN: 19990712  
 Last Updated on STN: 20000303  
 Entered Medline: 19990624  
 AB A set of 90 novel 2-(arylsulfonyl)-1,2,3, 4-tetrahydroisoquinoline -3-carboxylates and -hydroxamates as inhibitors of the matrix metalloproteinase human neutrophil collagenase (MMP-8) was designed, synthesized, and investigated by 3D-QSAR techniques (CoMFA, CoMSIA) and X-ray structure analysis. Docking studies of a reference compound are based on crystal structures of MMP-8 complexed with peptidic inhibitors to propose a model of its bioactive conformation. This model was validated by a 1.7 Å X-ray structure of the catalytic domain of MMP-8. The 3D-QSAR models based on a superposition rule derived from these docking studies were validated using conventional and cross-validated r<sup>2</sup> values using the leave-one-out method, repeated analyses using two randomly chosen cross-validation groups plus randomization of biological activities. This led to consistent and highly predictive 3D-QSAR models with good correlation coefficients for both CoMFA and CoMSIA, which were found to correspond to experimentally determined MMP-8 catalytic site topology in terms of steric, electrostatic, and hydrophobic complementarity. Subsets selected as smaller training sets using 2D fingerprints and maximum dissimilarity methods resulted in 3D-QSAR models with remarkable correlation coefficients and a high predictive power. This allowed to compensate the weaker zinc binding properties of carboxylates by introducing optimal fitting P1' residues. The final QSAR information agrees with all experimental data for the binding topology and thus provides clear guidelines and accurate activity predictions for novel MMP-8 inhibitors.  
 CT Check Tags: Comparative Study  
 \*Collagenases: AI, antagonists & inhibitors  
 Collagenases: CH, chemistry  
 Crystallography, X-Ray  
 Drug Design  
 Humans  
 Models, Molecular  
 Neutrophil Collagenase  
 \*Protease Inhibitors: CH, chemistry

## Protein Conformation

## Structure-Activity Relationship

CN 0 (Protease Inhibitors); EC 3.4.24.- (Collagenases); EC 3.4.24.34  
 (Neutrophil Collagenase)

L51 ANSWER 19 OF 85 MEDLINE on STN DUPLICATE 6  
 ACCESSION NUMBER: 93341313 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 8341137  
 TITLE: The phenytoin metabolite p-HPPH upregulates prostaglandin biosynthesis in human gingival fibroblasts challenged to interleukin-1.  
 AUTHOR: Brunius G; Iinuma M; Anduren I; Lerner U H; Modeer T  
 CORPORATE SOURCE: Department of Pedodontics, Faculty of Odontology, Karolinska Institutet, Huddinge, Sweden.  
 SOURCE: Life sciences, (1993) 53 (6) 503-15.  
 Journal code: 0375521. ISSN: 0024-3205.  
 PUB. COUNTRY: ENGLAND: United Kingdom  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 199308  
 ENTRY DATE: Entered STN: 19930917  
 Last Updated on STN: 19930917  
 Entered Medline: 19930831  
 ED Entered STN: 19930917  
 Last Updated on STN: 19930917  
 Entered Medline: 19930831  
 AB The effects of and interactions between the major phenytoin (PHT) metabolite 5-parahydroxyphenyl-5-phenylhydantoin (p-HPPH) and interleukin-1 (IL-1 alpha, IL-1 beta) or tumor necrosis factor alpha (TNF alpha) on prostaglandin biosynthesis in human gingival fibroblasts were studied. IL-1 alpha, IL-1 beta and TNF alpha, dose-dependently, stimulated PGE2 formation in gingival fibroblasts. The metabolite, p-HPPH (1.2-2.4 micrograms/ml), did not induce PGE2 formation itself but potentiated IL-1 alpha and IL1 beta induced PGE2 formation in the gingival fibroblasts in a manner dependent on the concentration of both IL-1 and p-HPPH. The metabolite also stimulated IL-1 induced formation of 6-Keto PGF1 alpha, the stable breakdown product of PGF2, in a dose dependent manner. IL-1 beta induces release of [3H]-arachidonic acid ([3H]-AA) from prelabelled fibroblasts, which was potentiated by p-HPPH (> or = 1.2 micrograms/ml). TNF alpha (> or = 1 ng/ml) significantly stimulated the biosynthesis of PGE2 by a process that was also potentiated by p-HPPH. Addition of exogenous, unlabelled AA (10 microM) caused an increase of PGE2 formation in the fibroblasts that was not potentiated by p-HPPH (1.6 micrograms/ml). The results indicate that treatment with p-HPPH results in upregulation of prostaglandin synthesis in gingival fibroblasts challenged to IL-1 or TNF alpha at the level of phospholipase A2.  
 CT Check Tags: Female; Male  
 Cells, Cultured  
 Child  
 Drug Synergism  
 Fibroblasts: ME, metabolism  
 Gingiva: CY, cytology  
 \*Gingiva: DE, drug effects  
 Gingiva: ME, metabolism  
 Humans  
 \*Interleukin-1: PD, pharmacology  
 \*Phenytoin: AA, analogs & derivatives  
 Phenytoin: PD, pharmacology

\*Prostaglandins: BI, biosynthesis  
 Research Support, Non-U.S. Gov't  
 \*Tumor Necrosis Factor-alpha: PD, pharmacology  
 Up-Regulation: DE, drug effects

RN 2784-27-2 (hydroxyphenytoin); 57-41-0 (Phenytoin)  
 CN 0 (Interleukin-1); 0 (Prostaglandins); 0 (Tumor Necrosis Factor-alpha)

L51 (ANSWER 20 OF 85 MEDLINE on STN  
 ACCESSION NUMBER: 2002652986 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 12411982  
 TITLE: Plasma levels of TNF-alpha and IL-6 are inversely related to cytochrome P450-dependent drug metabolism in patients with congestive heart failure.  
 AUTHOR: Frye Reginald F; Schneider Virginia M; Frye Carole S; Feldman Arthur M  
 CORPORATE SOURCE: Department of Pharmaceutical Sciences and Pharmacodynamic Research Center, School of Pharmacy, University of Pittsburgh, Pittsburgh, Pennsylvania 15261, USA.  
 SOURCE: Journal of cardiac failure, (2002 Oct) 8 (5) 315-9.  
 Journal code: 9442138. ISSN: 1071-9164.  
 PUB. COUNTRY: United States  
 DOCUMENT TYPE: (EVALUATION STUDIES)  
 Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200303  
 ENTRY DATE: Entered STN: 20021105  
 Last Updated on STN: 20030306  
 Entered Medline: 20030305

ED Entered STN: 20021105  
 Last Updated on STN: 20030306  
 Entered Medline: 20030305

AB BACKGROUND: Cytochrome P450 (CYP) enzymes are important mediators of drug metabolism, and activity of these enzymes is a major determinant of the duration and intensity of drug effect. Circulating plasma concentrations of pro-inflammatory cytokines (e.g., tumor necrosis factor [TNF]-alpha and interleukin [IL]-6) are elevated in patients with heart failure and these cytokines have been shown to down-regulate CYP enzyme activity. The purpose of this study was to evaluate the relationship between plasma cytokine concentrations and CYP enzyme activities in patients with heart failure. METHODS AND RESULTS: Sixteen patients with congestive heart failure (New York Heart Association classes II-IV) received a metabolic probe cocktail consisting of caffeine, mephenytoin, dextromethorphan, and chlorzoxazone to assess the activities of the CYP enzymes 1A2, 2C19, 2D6, and 2E1. Blood and urine samples were collected for drug and metabolite determinations by high-performance liquid chromatography (HPLC); cytokine concentrations were measured by enzyme-linked immunosorbent assay (ELISA). We found a striking inverse relationship between both TNF-alpha and IL-6 plasma concentrations and the activity of CYP2C19; metabolism of caffeine (CYP1A2) also had a negative association with IL-6 plasma concentrations. CONCLUSIONS: Cytokine-mediated decreases in drug metabolism may contribute to observed variability in drug response and augment the risk of adverse drug effects in CHF patients.

CT Check Tags: Female; Male  
 Adult  
 Aged  
 Biological Markers: BL, blood  
 Cytochrome P-450 Enzyme System: DE, drug effects

Cytochrome P-450 Enzyme System: GE, genetics  
 \*Cytochrome P-450 Enzyme System: ME, metabolism  
 Dextromethorphan: PD, pharmacology  
 Excitatory Amino Acid Antagonists: PD, pharmacology  
 Genetic Markers: DE, drug effects  
 Genetic Markers: GE, genetics  
 Genotype  
 Heart Failure, Congestive: GE, genetics  
 \*Heart Failure, Congestive: ME, metabolism  
 Humans  
 \*Interleukin-6: BL, blood  
     \*Mephenytoin: AA, analogs & derivatives  
 Mephenytoin: PD, pharmacology  
 Middle Aged  
 Mutation: DE, drug effects  
 Mutation: GE, genetics  
 Phenotype  
 Polymorphism, Genetic  
 Prevalence  
 Research Support, Non-U.S. Gov't  
 Statistics  
     \*Tumor Necrosis Factor-alpha: ME, metabolism

RN 125-71-3 (Dextromethorphan); 50-12-4 (Mephenytoin); 61837-65-8  
     (4-hydroxymephenytoin); 9035-51-2 (Cytochrome P-450 Enzyme System)  
 CN 0 (Biological Markers); 0 (Excitatory Amino Acid Antagonists); 0 (Genetic  
     Markers); 0 (Interleukin-6); 0 (Tumor Necrosis  
     Factor-alpha)

L51 ANSWER 21 OF 85 MEDLINE on STN  
 ACCESSION NUMBER: 96251432 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 8653494  
 TITLE: Effect of phenytoin on interleukin-1 beta production in  
     human gingival fibroblasts challenged to tumor  
     necrosis factor alpha in vitro.  
 AUTHOR: Brunius G; Yucel-Lindberg T; Shinoda K; Modeer T  
 CORPORATE SOURCE: Department of Orthodontics and Pediatric Dentistry, Faculty  
     of Odontology, Karolinska Institutet, Huddinge, Sweden.  
 SOURCE: European journal of oral sciences, (1996 Feb) 104 (1)  
     27-33.  
     Journal code: 9504563. ISSN: 0909-8836.  
 PUB. COUNTRY: Denmark  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Dental Journals; Priority Journals  
 ENTRY MONTH: 199608  
 ENTRY DATE: Entered STN: 19960808  
     Last Updated on STN: 19970203  
     Entered Medline: 19960801  
 ED Entered STN: 19960808  
     Last Updated on STN: 19970203  
     Entered Medline: 19960801  
 AB Effects and interaction of tumor necrosis factor alpha  
     (TNF alpha) and the antiepileptic drug phenytoin (PHT) on  
     interleukin-1 beta (IL-1 beta) production as well as on prostaglandin E2  
     (PGE2) formation were studied in gingival fibroblasts in vitro.  
     TNF alpha, in contrast to PHT, dose-dependently stimulated the  
     production of cell-associated IL-1 beta. The stimulatory effect of  
     TNF alpha on IL-1 beta production was accompanied by enhanced PGE2  
     formation. When PHT and TNF alpha were added simultaneously,  
     the drug potentiated the stimulatory effect of TNF alpha on both

IL-1 beta production and PGE2 formation. The major PHT metabolite, p-HPPH, did not affect IL-1 beta production, either alone or in combination with TNF alpha. The production of IL-1 beta induced by TNF alpha and the combination of TNF alpha and PHT was further enhanced in the presence of the prostaglandin endoperoxide (PGH) synthase inhibitors, indomethacin and flurbiprofen. The PHT-mediated enhancement of TNF alpha-induced IL-1 beta production and PGE2 formation in gingival fibroblasts may be an important link in the pathogenesis of gingival overgrowth induced by PHT.

CT

Child

Cyclooxygenase Inhibitors: ME, metabolism

Cyclooxygenase Inhibitors: PD, pharmacology

Dinoprostone: BI, biosynthesis

Dose-Response Relationship, Drug

Drug Synergism

Fibroblasts: DE, drug effects

Fibroblasts: ME, metabolism

Flurbiprofen: PD, pharmacology

Gingiva: CY, cytology

\*Gingiva: DE, drug effects

Gingiva: ME, metabolism

Gingival Hyperplasia: CI, chemically induced

Gingival Hyperplasia: ME, metabolism

Humans

Indomethacin: PD, pharmacology

\*Interleukin-1: BI, biosynthesis

**Phenytoin: AA, analogs & derivatives**

\*Phenytoin: PD, pharmacology

Research Support, Non-U.S. Gov't

**\*Tumor Necrosis Factor-alpha: PD, pharmacology**

Up-Regulation

RN 2784-27-2 (hydroxyphenytoin); 363-24-6 (Dinoprostone); 5104-49-4  
(Flurbiprofen); 53-86-1 (Indomethacin); 57-41-0 (Phenytoin)CN 0 (Cyclooxygenase Inhibitors); 0 (Interleukin-1); 0 (**Tumor**  
**Necrosis Factor-alpha**)

L51 ANSWER 22 OF 85 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN DUPLICATE 1

ACCESSION NUMBER: 2004378690 EMBASE

TITLE: The evolution of the matrix metalloproteinase inhibitor drug discovery program at Abbott Laboratories.

AUTHOR: Wada C.K.

CORPORATE SOURCE: C.K. Wada, Abbott Laboratories, Dept. R47J, 100 Abbott Park Rd., Abbott Park, IL 60064-6100, United States.  
carol.k.wada@abbott.com

SOURCE: Current Topics in Medicinal Chemistry, (2004) Vol. 4, No. 12, pp. 1255-1267.

Refs: 24

ISSN: 1568-0266 CODEN: CTMCL

COUNTRY: Netherlands

DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 016 Cancer  
029 Clinical Biochemistry  
030 Pharmacology  
037 Drug Literature Index  
052 Toxicology

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 20040924

Last Updated on STN: 20040924

ED Entered STN: 20040924

Last Updated on STN: 20040924

AB **Matrix metalloproteinases (MMPs)** have been implicated in several pathologies. At Abbott Laboratories, the **matrix metalloproteinases** inhibitor drug discovery program has focused on the discovery of a potent, selective, orally bioavailable **MMP** inhibitor for the treatment of cancer. The program evolved from early succinate-based inhibitors to utilizing in-house technology such as SAR by NMR to develop a novel class of biaryl **hydroxamate MMP** inhibitors. The metabolic instability of the biaryl **hydroxamates** led to the discovery of a new class of N-formylhydroxylamine (**retrohydroxamate**) biaryl ethers, exemplified by ABT-770 (16). Toxicity issues with this pre-clinical candidate led to the discovery of another novel class of **retrohydroxamate MMP** inhibitors, the **phenoxyphenyl sulfones** such as ABT-518 (19j). ABT-518 is a potent, orally bioavailable, selective inhibitor of **MMP-2** and 9 over **MMP-1** that has been evaluated in Phase I clinical trials in cancer patients. .COPYRGT. 2004 Bentham Science Publishers Ltd.

CT Medical Descriptors:

enzyme inhibition  
drug structure  
drug synthesis  
drug design  
structure activity relation  
structure analysis  
drug selectivity  
drug bioavailability  
drug potency  
nuclear magnetic resonance  
drug classification  
drug half life  
in vitro study  
in vivo study  
melanoma: DT, drug therapy  
antineoplastic activity  
cancer inhibition  
cancer model  
drug clearance  
toxicity testing  
human  
nonhuman  
mouse  
clinical trial  
review

Drug Descriptors:

\*matrix metalloproteinase inhibitor: CT, clinical trial  
\*matrix metalloproteinase inhibitor: AN, drug analysis  
\*matrix metalloproteinase inhibitor: CM, drug comparison  
\*matrix metalloproteinase inhibitor: DV, drug development  
\*matrix metalloproteinase inhibitor: DT, drug therapy  
\*matrix metalloproteinase inhibitor: TO, drug toxicity  
\*matrix metalloproteinase inhibitor: PK, pharmacokinetics  
\*matrix metalloproteinase inhibitor: PD, pharmacology  
\*matrix metalloproteinase inhibitor: IV, intravenous drug administration  
\*matrix metalloproteinase inhibitor: PO, oral drug administration  
succinic acid derivative: CT, clinical trial  
succinic acid derivative: AN, drug analysis

succinic acid derivative: CM, drug comparison  
succinic acid derivative: DV, drug development  
succinic acid derivative: DT, drug therapy  
succinic acid derivative: PK, pharmacokinetics  
succinic acid derivative: PD, pharmacology  
succinic acid derivative: IV, intravenous drug administration  
succinic acid derivative: PO, oral drug administration  
hydroxamic acid derivative: CT, clinical trial  
hydroxamic acid derivative: AN, drug analysis  
hydroxamic acid derivative: CM, drug comparison  
hydroxamic acid derivative: DV, drug development  
hydroxamic acid derivative: DT, drug therapy  
hydroxamic acid derivative: PK, pharmacokinetics  
hydroxamic acid derivative: PD, pharmacology  
hydroxamic acid derivative: IV, intravenous drug administration  
hydroxamic acid derivative: PO, oral drug administration  
gelatinase A: EC, endogenous compound  
gelatinase B: EC, endogenous compound  
interstitial collagenase: EC, endogenous compound  
matrilysin: EC, endogenous compound  
abt 770: AN, drug analysis  
abt 770: CM, drug comparison  
abt 770: DV, drug development  
abt 770: DT, drug therapy  
abt 770: TO, drug toxicity  
abt 770: PK, pharmacokinetics  
abt 770: PD, pharmacology  
abt 770: IV, intravenous drug administration  
abt 770: PO, oral drug administration  
abt 518: CT, clinical trial  
abt 518: AN, drug analysis  
abt 518: CM, drug comparison  
abt 518: DV, drug development  
abt 518: DT, drug therapy  
abt 518: PK, pharmacokinetics  
abt 518: PD, pharmacology  
abt 518: PO, oral drug administration  
metalloproteinase inhibitor: CT, clinical trial  
metalloproteinase inhibitor: AN, drug analysis  
metalloproteinase inhibitor: CM, drug comparison  
metalloproteinase inhibitor: DV, drug development  
metalloproteinase inhibitor: DT, drug therapy  
metalloproteinase inhibitor: TO, drug toxicity  
metalloproteinase inhibitor: PK, pharmacokinetics  
metalloproteinase inhibitor: PD, pharmacology  
metalloproteinase inhibitor: IV, intravenous drug administration  
metalloproteinase inhibitor: PO, oral drug administration  
batimastat: AN, drug analysis  
batimastat: CM, drug comparison  
batimastat: DV, drug development  
batimastat: PK, pharmacokinetics  
batimastat: PD, pharmacology  
batimastat: IV, intravenous drug administration  
batimastat: PO, oral drug administration  
macrocyclic compound: AN, drug analysis  
macrocyclic compound: CM, drug comparison  
macrocyclic compound: DV, drug development  
macrocyclic compound: PD, pharmacology  
macrocyclic compound: IV, intravenous drug administration  
indole derivative: AN, drug analysis

indole derivative: CM, drug comparison  
 indole derivative: DV, drug development  
 indole derivative: PD, pharmacology  
 ketone derivative: AN, drug analysis  
 ketone derivative: CM, drug comparison  
 ketone derivative: DV, drug development  
 ketone derivative: PD, pharmacology  
 ketone derivative: IV, intravenous drug administration  
 pyrrole derivative: AN, drug analysis  
 pyrrole derivative: CM, drug comparison  
 pyrrole derivative: DV, drug development  
 pyrrole derivative: PD, pharmacology  
 benzophenone: AN, drug analysis  
 benzophenone: CM, drug comparison  
 benzophenone: DV, drug development  
 benzophenone: PD, pharmacology  
 stromelysin inhibitor: AN, drug analysis  
 stromelysin inhibitor: CM, drug comparison  
 stromelysin inhibitor: DV, drug development

## CT Drug Descriptors:

stromelysin inhibitor: PD, pharmacology  
 stromelysin: EC, endogenous compound  
 hydantoin derivative: AN, drug analysis  
 hydantoin derivative: CM, drug comparison  
 hydantoin derivative: DV, drug development  
 hydantoin derivative: PK, pharmacokinetics  
 hydantoin derivative: PD, pharmacology  
 hydantoin derivative: IV, intravenous drug administration  
 hydantoin derivative: PO, oral drug administration  
 neutrophil collagenase: EC, endogenous compound  
 collagenase 3: EC, endogenous compound  
 unclassified drug

RN (gelatinase A) 146480-35-5; (gelatinase B) 146480-36-6; (matrilysin)  
 141256-52-2; (batimastat) 130370-60-4, 130464-84-5; (benzophenone)  
 119-61-9; (stromelysin) 79955-99-0; (collagenase 3) 175449-82-8

CN (1) Abt 770; (2) Abt 518

CO (2) Abbott

L51 ANSWER 23 OF 85 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STM

ACCESSION NUMBER: 2005090790 EMBASE

TITLE: Recent developments in the design of specific matrix metalloproteinase inhibitors aided by structural and computational studies.

AUTHOR: Rao B.G.

CORPORATE SOURCE: B.G. Rao, Vertex Pharmaceuticals Incorporated, 130 Waverly Street, Cambridge, MA 02139, United States.  
[govinda\\_rao@vrtx.com](mailto:govinda_rao@vrtx.com)

SOURCE: Current Pharmaceutical Design, (2005) Vol. 11, No. 3, pp. 295-322.

Refs: 133

ISSN: 1381-6128 CODEN: CPDEFP

COUNTRY: Netherlands

DOCUMENT TYPE: Journal; General Review

FILE SEGMENT:  
 016 Cancer  
 029 Clinical Biochemistry  
 030 Pharmacology  
 031 Arthritis and Rheumatism  
 037 Drug Literature Index  
 038 Adverse Reactions Titles

LANGUAGE: English  
SUMMARY LANGUAGE: English  
ENTRY DATE: Entered STN: 20050310  
Last Updated on STN: 20050310

ED    Entered STN: 20050310  
Last Updated on STN: 20050310

AB    It has been 10 years since a 3-dimensional structure of the catalytic domain of a **Matrix Metalloprotease (MMP)** was revealed for the first time in 1994. More than 80 structures of different **MMPs** in apo and inhibited forms, determined by X-ray crystallography and NMR methods, have been published by the end of year 2003. A large number of very potent inhibitors have been disclosed in published and patent literature. Several **MMP** inhibitors entered clinical trials for the treatment of cancer and arthritis. Most of the first generation inhibitors have **hydroxamic acid** as the Zinc-binding group and have limited specificity. With the failure of these inhibitors in clinical trials, more efforts have been directed to the design of specific inhibitors with different Zn-binding groups in recent years. This review will summarize all the published structural information and focus on the inhibitors that were designed to take advantage of the nonprime side of the **MMP** active site using structural information and computational analysis. Representative structures from all **MMPs** are aligned to a target structure to provide a better understanding of the similarities and differences of the active site pockets. This analysis supports the view that the differences in the nonprime side pockets provide better opportunities for designing inhibitors with higher specificity. Published information on all the Zinc-binding groups of **MMP** inhibitors is reviewed for the first time. Pros and cons of inhibitors with non-**hydroxamate** Zinc-binding groups in terms of specificity, toxicity and pharmacokinetic properties are discussed. .COPYRGT. 2005 Bentham Science Publishers Ltd.

CT    Medical Descriptors:  
\*computer aided design  
\*drug design  
drug structure  
structure analysis  
computer analysis  
three dimensional imaging  
protein domain  
X ray crystallography  
nuclear magnetic resonance  
cancer chemotherapy  
arthritis: DT, drug therapy  
drug binding  
binding site  
drug specificity  
drug targeting  
protein targeting  
pancreas cancer: DT, drug therapy  
osteoarthritis: DT, drug therapy  
solid tumor: DT, drug therapy  
musculoskeletal disease: SI, side effect  
arthralgia: SI, side effect  
myalgia: SI, side effect  
Kaposi sarcoma: DT, drug therapy  
drug half life  
drug selectivity  
human  
clinical trial  
review

priority journal

Drug Descriptors:

\*matrix metalloproteinase inhibitor: AE, adverse drug reaction  
\*matrix metalloproteinase inhibitor: CT, clinical trial  
\*matrix metalloproteinase inhibitor: AN, drug analysis  
\*matrix metalloproteinase inhibitor: CM, drug comparison  
\*matrix metalloproteinase inhibitor: DV, drug development  
\*matrix metalloproteinase inhibitor: DT, drug therapy  
\*matrix metalloproteinase inhibitor: TO, drug toxicity  
\*matrix metalloproteinase inhibitor: PK, pharmacokinetics  
\*matrix metalloproteinase inhibitor: PD, pharmacology  
\*matrix metalloproteinase inhibitor: PO, oral drug administration  
matrix metalloproteinase: EC, endogenous compound

hydroxamic acid

zinc

collagenase: EC, endogenous compound  
gelatinase A: EC, endogenous compound  
stromelysin: EC, endogenous compound  
matrilysin: EC, endogenous compound  
gelatinase B: EC, endogenous compound  
stromelysin 3: EC, endogenous compound  
stromelysin 2: EC, endogenous compound  
macrophage elastase: EC, endogenous compound  
collagenase 3: EC, endogenous compound

batimastat: AE, adverse drug reaction  
batimastat: CT, clinical trial  
batimastat: AN, drug analysis  
batimastat: CM, drug comparison  
batimastat: DT, drug therapy  
batimastat: PO, oral drug administration

marimastat: AE, adverse drug reaction  
marimastat: CT, clinical trial  
marimastat: AN, drug analysis  
marimastat: CM, drug comparison  
marimastat: DT, drug therapy

solimastat: CT, clinical trial  
solimastat: AN, drug analysis  
solimastat: CM, drug comparison  
solimastat: DT, drug therapy  
prinomastat: CT, clinical trial  
prinomastat: AN, drug analysis  
prinomastat: CM, drug comparison  
prinomastat: DT, drug therapy

cgs 27023a: AE, adverse drug reaction  
cgs 27023a: CT, clinical trial  
cgs 27023a: AN, drug analysis  
cgs 27023a: CM, drug comparison  
cgs 27023a: DT, drug therapy

cipemastat: CT, clinical trial  
cipemastat: AN, drug analysis  
cipemastat: CM, drug comparison  
cipemastat: DT, drug therapy

4 [[[4 (4 chlorophenoxy)phenyl]sulfonyl]methyl]tetrahydro 2h pyran 4  
carbohydroxamic acid: CT, clinical trial  
4 [[[4 (4 chlorophenoxy)phenyl]sulfonyl]methyl]tetrahydro 2h pyran 4  
carbohydroxamic acid: AN, drug analysis  
4 [[[4 (4 chlorophenoxy)phenyl]sulfonyl]methyl]tetrahydro 2h pyran 4  
carbohydroxamic acid: CM, drug comparison  
4 [[[4 (4 chlorophenoxy)phenyl]sulfonyl]methyl]tetrahydro 2h pyran 4  
carbohydroxamic acid: DT, drug therapy

tanomastat: CT, clinical trial  
 tanomastat: AN, drug analysis  
 tanomastat: CM, drug comparison  
 tanomastat: DT, drug therapy  
 d 2163: CT, clinical trial  
 d 2163: AN, drug analysis  
 d 2163: CM, drug comparison  
 d 2163: DT, drug therapy  
 4 dedimethylaminosacycline: CT, clinical trial  
 4 dedimethylaminosacycline: AN, drug analysis  
 4 dedimethylaminosacycline: CM, drug comparison  
 4 dedimethylaminosacycline: DT, drug therapy  
 abt 518: CT, clinical trial  
 abt 518: AN, drug analysis  
 abt 518: CM, drug comparison  
 abt 518: DT, drug therapy  
 abt 518: PK, pharmacokinetics  
 s 3304: CT, clinical trial  
 s 3304: AN, drug analysis  
 s 3304: CM, drug comparison  
 s 3304: DT, drug therapy  
 antineoplastic agent: CT, clinical trial  
 antineoplastic agent: AN, drug analysis  
 antineoplastic agent: CM, drug comparison  
 antineoplastic agent: DT, drug therapy  
 antineoplastic agent: PK, pharmacokinetics  
 tetracycline derivative: CT, clinical trial  
 tetracycline derivative: DT, drug therapy  
 fibronectin: EC, endogenous compound  
 zinc ion: EC, endogenous compound  
 unindexed drug  
 unclassified drug

RN (zinc) 7440-66-6; (collagenase) 37288-86-1, 39433-96-0, 9001-12-1;  
 (gelatinase A) 146480-35-5; (stromelysin) 79955-99-0; (matrilysin)  
 141256-52-2; (gelatinase B) 146480-36-6; (stromelysin 3) 145267-01-2;  
 (stromelysin 2) 140610-48-6; (collagenase 3) 175449-82-8; (batimastat)  
 130370-60-4, 130464-84-5; (marimastat) 154039-60-8; (prinomastat)  
 192329-42-3, 195008-93-6; (cgs 27023a) 169799-04-6; (cipemastat)  
 190648-49-8; (4 [[4 (4 chlorophenoxy)phenyl  
 ]sulfonyl]methyl]tetrahydro 2h pyran 4 carbohydroxamic acid) 193022-04-7;  
 (tanomastat) 179545-76-7, 179545-77-8; (d 2163) 191537-76-5; (4  
 dedimethylaminosacycline) 15866-90-7; (fibronectin) 86088-83-7; (zinc  
 ion) 23713-49-7  
 CN (1) Bb 94; (2) Bb 2516; (3) Bb 3644; (4) Ag 3340; (5) Cgs 27023a; (6) Ro  
 32 3555; (7) Rs 130830; (8) Abt 518; (9) Bay 12 9566; (10) S 3304  
 CO (3) British Biotechnology; (4) Agouron; (5) Novartis; (7) Hoffmann La  
 Roche; (8) Abbott; (9) Bayer; (10) Shionogi

L51 ANSWER 24 OF 85... EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights  
 reserved on STN

ACCESSION NUMBER: 2004378692 EMBASE  
 TITLE: The design and synthesis of aryl hydroxamic acid  
 inhibitors of MMPs and TACE.  
 AUTHOR: Levin J.I.  
 CORPORATE SOURCE: J.I. Levin, Wyeth Research, 401 N. Middletown Road, Pearl  
 River, NY 10965, United States. levinji@wyeth.com  
 SOURCE: Current Topics in Medicinal Chemistry, (2004) Vol. 4, No.  
 12, pp. 1289-1310.  
 Refs: 60  
 ISSN: 1568-0266 CODEN: CTMCL

COUNTRY: Netherlands  
DOCUMENT TYPE: Journal; General Review  
FILE SEGMENT:  
016 Cancer  
029 Clinical Biochemistry  
030 Pharmacology  
031 Arthritis and Rheumatism  
037 Drug Literature Index  
038 Adverse Reactions Titles  
LANGUAGE: English  
SUMMARY LANGUAGE: English  
ENTRY DATE: Entered STN: 20040924  
Last Updated on STN: 20040924  
ED Entered STN: 20040924  
Last Updated on STN: 20040924  
AB Three different classes of aryl **hydroxamic acid** scaffolds have been explored and provided potent inhibitors of **MMP-1, -2, -9, -13** and **TACE**. Structure-based design has allowed the evolution of these inhibitors from broad spectrum inhibitors into compounds that are more selective for **MMPs** relevant to particular disease states. Aryl **hydroxamates** selective for **MMP-9, MMP-13** and **TACE** have been disclosed that may aid in the study of the physiological role of these enzymes. Furthermore, the different selectivity profiles offered by these **MMP/TACE** inhibitors may allow the determination of which metalloprotease, or group of metalloproteases, must be inhibited for the safe, long-term treatment of osteoarthritis, rheumatoid arthritis and cancer. Some of these compounds have demonstrated useful biological activity in efficacy models relevant to osteoarthritis and rheumatoid arthritis and are therefore potential clinical candidates. .COPYRGT. 2004 Bentham Science Publishers Ltd.  
CT Medical Descriptors:  
drug design  
drug synthesis  
enzyme inhibition  
drug structure  
structure analysis  
drug potency  
drug selectivity  
drug safety  
long term care  
osteoarthritis: DT, drug therapy  
rheumatoid arthritis: DT, drug therapy  
cancer therapy  
drug efficacy  
cancer inhibition  
antineoplastic activity  
musculoskeletal disease: SI, side effect  
structure activity relation  
high throughput screening  
human  
nonhuman  
mouse  
clinical trial  
review  
Drug Descriptors:  
\*hydroxamic acid derivative: AE, adverse drug reaction  
\*hydroxamic acid derivative: CT, clinical trial  
\*hydroxamic acid derivative: AN, drug analysis  
\*hydroxamic acid derivative: CM, drug comparison  
\*hydroxamic acid derivative: DV, drug development

\*hydroxamic acid derivative: DT, drug therapy  
\*hydroxamic acid derivative: PD, pharmacology  
\*hydroxamic acid derivative: IP, intraperitoneal drug administration  
    \*hydroxamic acid derivative: PO, oral drug administration  
    \*matrix metalloproteinase inhibitor: AE, adverse drug reaction  
    \*matrix metalloproteinase inhibitor: CT, clinical trial  
    \*matrix metalloproteinase inhibitor: AN, drug analysis  
    \*matrix metalloproteinase inhibitor: CM, drug comparison  
    \*matrix metalloproteinase inhibitor: DV, drug development  
    \*matrix metalloproteinase inhibitor: DT, drug therapy  
    \*matrix metalloproteinase inhibitor: PD, pharmacology  
    \*matrix metalloproteinase inhibitor: IP, intraperitoneal drug administration  
        \*matrix metalloproteinase inhibitor: PO, oral drug administration  
            \*tumor necrosis factor alpha converting enzyme inhibitor: AN, drug analysis  
                \*tumor necrosis factor alpha converting enzyme inhibitor: CM, drug comparison  
                \*tumor necrosis factor alpha converting enzyme inhibitor: DV, drug development  
                \*tumor necrosis factor alpha converting enzyme inhibitor: DT, drug therapy  
                \*tumor necrosis factor alpha converting enzyme inhibitor: PD, pharmacology  
                \*tumor necrosis factor alpha converting enzyme inhibitor: PO, oral drug administration  
                    matrix metalloproteinase: EC, endogenous compound  
                        tumor necrosis factor alpha converting enzyme: EC, endogenous compound  
interstitial collagenase: EC, endogenous compound  
gelatinase A: EC, endogenous compound  
gelatinase B: EC, endogenous compound  
collagenase 3: EC, endogenous compound  
stromelysin inhibitor: AE, adverse drug reaction  
stromelysin inhibitor: CT, clinical trial  
stromelysin inhibitor: AN, drug analysis  
stromelysin inhibitor: CM, drug comparison  
stromelysin inhibitor: DT, drug therapy  
stromelysin inhibitor: PD, pharmacology  
cgs 27023a: AE, adverse drug reaction  
cgs 27023a: CT, clinical trial  
cgs 27023a: AN, drug analysis  
cgs 27023a: CM, drug comparison  
cgs 27023a: DT, drug therapy  
cgs 27023a: PD, pharmacology  
cgs 27023a: PO, oral drug administration  
marimastat: AE, adverse drug reaction  
marimastat: CT, clinical trial  
marimastat: AN, drug analysis  
marimastat: CM, drug comparison  
marimastat: DT, drug therapy  
marimastat: PD, pharmacology  
    cipemastat: AE, adverse drug reaction  
    cipemastat: CT, clinical trial  
    cipemastat: AN, drug analysis  
    cipemastat: CM, drug comparison  
    cipemastat: DT, drug therapy  
    cipemastat: PD, pharmacology  
prinomastat: AE, adverse drug reaction  
prinomastat: CT, clinical trial

prinomastat: AN, drug analysis  
prinomastat: CM, drug comparison  
prinomastat: DT, drug therapy  
prinomastat: PD, pharmacology  
anthranilic acid derivative: AE, adverse drug reaction  
anthranilic acid derivative: CT, clinical trial  
anthranilic acid derivative: AN, drug analysis  
anthranilic acid derivative: CM, drug comparison  
anthranilic acid derivative: DT, drug therapy  
anthranilic acid derivative: PD, pharmacology  
anthranilic acid derivative: IP, intraperitoneal drug administration  
piperidine derivative: AN, drug analysis  
piperidine derivative: CM, drug comparison  
piperidine derivative: DV, drug development  
piperidine derivative: PD, pharmacology  
piperazine derivative: AN, drug analysis  
piperazine derivative: CM, drug comparison  
piperazine derivative: DV, drug development  
piperazine derivative: PD, pharmacology  
sulfonamide: AN, drug analysis  
sulfonamide: CM, drug comparison  
sulfonamide: DV, drug development  
sulfonamide: PD, pharmacology  
sulfonamide: PO, oral drug administration  
aniline derivative: AN, drug analysis  
aniline derivative: CM, drug comparison  
aniline derivative: DV, drug development  
aniline derivative: PD, pharmacology  
pyridine derivative: AN, drug analysis  
pyridine derivative: CM, drug comparison  
pyridine derivative: DV, drug development  
pyridine derivative: PD, pharmacology  
thiophene derivative: AN, drug analysis  
thiophene derivative: CM, drug comparison  
thiophene derivative: DV, drug development  
thiophene derivative: PD, pharmacology

## CT Drug Descriptors:

pyrazole derivative: AN, drug analysis  
pyrazole derivative: CM, drug comparison  
pyrazole derivative: DV, drug development  
pyrazole derivative: PD, pharmacology  
cyclohexane derivative: AN, drug analysis  
cyclohexane derivative: CM, drug comparison  
cyclohexane derivative: DV, drug development  
cyclohexane derivative: PD, pharmacology  
quinoline derivative: AN, drug analysis  
quinoline derivative: CM, drug comparison  
quinoline derivative: DV, drug development  
quinoline derivative: PD, pharmacology  
quinoline derivative: PO, oral drug administration  
isoxazole derivative: AN, drug analysis  
isoxazole derivative: CM, drug comparison  
isoxazole derivative: DV, drug development  
isoxazole derivative: PD, pharmacology  
isothiazole derivative: AN, drug analysis  
isothiazole derivative: CM, drug comparison  
isothiazole derivative: DV, drug development  
isothiazole derivative: PD, pharmacology  
pyrazolopyrimidine derivative: AN, drug analysis  
pyrazolopyrimidine derivative: CM, drug comparison

pyrazolopyrimidine derivative: DV, drug development  
 pyrazolopyrimidine derivative: PD, pharmacology  
 benzofuran derivative: AN, drug analysis  
 benzofuran derivative: CM, drug comparison  
 benzofuran derivative: DV, drug development  
 benzofuran derivative: PD, pharmacology  
 benzothiophene derivative: AN, drug analysis  
 benzothiophene derivative: CM, drug comparison  
 benzothiophene derivative: DV, drug development  
 benzothiophene derivative: PD, pharmacology  
 unindexed drug  
**RN**      (tumor necrosis factor alpha  
           converting enzyme) 151769-16-3; (gelatinase A) 146480-35-5;  
           (gelatinase B) 146480-36-6; (collagenase 3) 175449-82-8; (cgs 27023a)  
           169799-04-6; (marimastat) 154039-60-8; (cipemastat) 190648-49-8;  
           (prinomastat) 192329-42-3, 195008-93-6  
**CN**      Cgs 27023a; Ro 32 3555; Ag 3340  
  
**L51**   ANSWER 25 OF 85 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights  
       reserved on STN  
**ACCESSION NUMBER:**   2004026493 EMBASE  
**TITLE:**            Cyclic sulfone hydroxamates as inhibitors of  
                   matrix metalloproteinases and/or  
                   TNF- $\alpha$  -converting enzymes.  
**SOURCE:**          Expert Opinion on Therapeutic Patents, (2004) Vol. 14, No.  
                   1, pp. 121-124.  
**Refs:**            15  
**ISSN:**            1354-3776   **CODEN:** EOTPEG  
**COUNTRY:**        United Kingdom  
**DOCUMENT TYPE:**   Journal; Article  
**FILE SEGMENT:**    016      Cancer  
                   030      Pharmacology  
                   031      Arthritis and Rheumatism  
                   037      Drug Literature Index  
**LANGUAGE:**        English  
**SUMMARY LANGUAGE:**   English  
**ENTRY DATE:**      Entered STN: 20040129  
                   Last Updated on STN: 20040129  
**ED**   Entered STN: 20040129  
       Last Updated on STN: 20040129  
**AB**   A series of cyclic sulfone-based hydroxamates are claimed to be  
       inhibitors of matrix metalloproteinases (MMPs  
       ) and TNF- $\alpha$  -converting enzyme (TACE). Synthesis of one representative example is described. No  
       biological data are given but these compounds are claimed to inhibit  
       MMPs, TACE and aggrecanase. These compounds might be  
       useful to treat chronic diseases such as arthritis and cancer.  
**CT**   Medical Descriptors:  
       drug synthesis  
       chronic disease: DT, drug therapy  
       drug structure  
       osteoarthritis: DT, drug therapy  
       rheumatoid arthritis: DT, drug therapy  
       physical chemistry  
       patent  
       drug selectivity  
       drug mechanism  
       arthritis: DT, drug therapy  
       cancer chemotherapy  
       human

clinical trial

article

Drug Descriptors:

\*sulfone derivative: CT, clinical trial

\*sulfone derivative: AN, drug analysis

\*sulfone derivative: DV, drug development

\*sulfone derivative: DT, drug therapy

\*sulfone derivative: PD, pharmacology

\*hydroxamic acid derivative: CT, clinical trial

\*hydroxamic acid derivative: AN, drug analysis

\*hydroxamic acid derivative: DV, drug development

\*hydroxamic acid derivative: DT, drug therapy

\*hydroxamic acid derivative: PD, pharmacology

matrix metalloproteinase inhibitor: CT, clinical trial

matrix metalloproteinase inhibitor: AN, drug analysis

matrix metalloproteinase inhibitor: DV, drug development

matrix metalloproteinase inhibitor: DT, drug therapy

matrix metalloproteinase inhibitor: PD, pharmacology

prinomasta: AN, drug analysis

prinomasta: DV, drug development

prinomasta: PD, pharmacology

ro 327315: AN, drug analysis

ro 327315: DV, drug development

ro 327315: PD, pharmacology

dpc 333: CT, clinical trial

dpc 333: AN, drug analysis

dpc 333: DV, drug development

dpc 333: DT, drug therapy

dpc 333: PD, pharmacology

bms 561392: CT, clinical trial

bms 561392: AN, drug analysis

bms 561392: DV, drug development

bms 561392: DT, drug therapy

bms 561392: PD, pharmacology

tumor necrosis factor alpha converting enzyme inhibitor: CT, clinical trial

tumor necrosis factor alpha converting enzyme inhibitor: AN, drug analysis

tumor necrosis factor alpha converting enzyme inhibitor: DV, drug development

tumor necrosis factor alpha converting enzyme inhibitor: DT, drug therapy

tumor necrosis factor alpha converting enzyme inhibitor: PD, pharmacology

matrix metalloproteinase: EC, endogenous compound

tumor necrosis factor alpha converting enzyme: EC, endogenous compound

aggrecanase: EC, endogenous compound

etanercept: PD, pharmacology

infliximab: PD, pharmacology

adalimumab: PD, pharmacology

tumor necrosis factor antibody: PD, pharmacology

tumor necrosis factor antibody: PO, oral drug administration

marimastat: AN, drug analysis

marimastat: DV, drug development

marimastat: PD, pharmacology

cipemastat: AN, drug analysis

cipemastat: DV, drug development

cipemastat: PD, pharmacology

4 [[4 (4 chlorophenoxy)phenyl]sulfonyl]methyl]tetrahydro 2h pyran 4

carbohydroxamic acid: AN, drug analysis  
 4 [[[4 (4 chlorophenoxy)phenyl]sulfonyl]methyl]tetrahydro 2h pyran 4  
 carbohydroxamic acid: DV, drug development  
 4 [[[4 (4 chlorophenoxy)phenyl]sulfonyl]methyl]tetrahydro 2h pyran 4  
 carbohydroxamic acid: PD, pharmacology  
 tanomastat: AN, drug analysis  
 tanomastat: DV, drug development  
 tanomastat: PD, pharmacology  
 d 2163: AN, drug analysis  
 d 2163: DV, drug development  
 d 2163: PD, pharmacology  
 unclassified drug  
 RN (tumor necrosis factor alpha  
 converting enzyme) 151769-16-3; (aggrecanase) 147172-61-0;  
 (etanercept) 185243-69-0, 200013-86-1; (infliximab) 170277-31-3;  
 (adalimumab) 331731-18-1; (tumor necrosis factor  
 antibody) 162774-06-3; (marimastat) 154039-60-8; (cipemastat) 190648-49-8;  
 (4 [[[4 (4 chlorophenoxy)phenyl]sulfonyl]methyl]tetrahydro 2h  
 pyran 4 carbohydroxamic acid) 193022-04-7; (tanomastat) 179545-76-7,  
 179545-77-8; (d 2163) 191537-76-5  
 CN (1) Enbrel; (2) Enbrel; (3) Remicade; (4) Bms 275291; (5) Bms 561392; (6)  
 D 2163; Rs 130830; Bay 129566; Ro 327315; Dpc 333  
 CO (1) Amgen; (2) Wyeth; (3) Centocor; (6) Bristol Myers Squibb

L51 ANSWER 26 OF 85 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2003193795 EMBASE  
 TITLE: Matrix metalloproteinase inhibitors  
 (MMPIs): The beginning of phase I or the termination of  
 phase III clinical trials.  
 AUTHOR: Pavlaki M.; Zucker S.  
 CORPORATE SOURCE: M. Pavlaki, Department of Medicine, School of Medicine,  
 Stt. Univ. of NY at Stony Brook, Stony Brook, NY 11794,  
 United States. s\_zucker@yahoo.com  
 SOURCE: Cancer and Metastasis Reviews, (2003) Vol. 22, No. 2-3, pp.  
 177-203.  
 Refs: 210  
 ISSN: 0167-7659 CODEN: CMRED4  
 COUNTRY: Netherlands  
 DOCUMENT TYPE: Journal; General Review  
 FILE SEGMENT: 016 Cancer  
 030 Pharmacology  
 037 Drug Literature Index  
 038 Adverse Reactions Titles  
 LANGUAGE: English  
 SUMMARY LANGUAGE: English  
 ENTRY DATE: Entered STN: 20030529  
 Last Updated on STN: 20030529  
 ED Entered STN: 20030529  
 Last Updated on STN: 20030529  
 AB The decade of the 1990s was ripe with enthusiasm for the use of MMPIs to  
 treat cancer. Limitations to new cytotoxic chemotherapy approaches to  
 treat solid cancers and a better understanding of tumor biology provided a  
 strong impetus for alternative drug development. It is estimated that the  
 pharmaceutical industry invested at least a billion dollars in this  
 effort. Because MMPIs represent an entirely different therapeutic  
 modality from proven anti-cancer agents, many of the therapeutic trials  
 designed to test MMPIs in human patients with cancer bypassed traditional  
 approaches to evaluate drug efficiency. The concept of systematic  
 progression from small phase I (dose escalation to toxicity to examine

drug safety), to phase II (drug treatment of patients with cancer types considered to be good candidates for the selected drug), to phase III (randomized trial of new drug versus best available therapy to determine drug efficacy) trials was modified. Much to the chagrin of everyone involved in these studies, the randomized trials of MMPIs in advanced cancer have, pretty much, flopped. This review article will attempt to dissect out aspects of previous human and animal studies that may be helpful in making decisions about the future of MMPI drug development for the treatment of cancer. The important questions to be addressed in this report are: What are the lessons that we have learned from preclinical (animal models) and clinical studies of MMPIs in cancer? Are we ready to abandon MMPIs as a therapeutic modality in cancer (termination of phase III trials) or do we need to have a better understanding of the myriad effects of **MMPS** in cancer before we proceed to develop different types of drugs that alter **MMPI** activity in patients with cancer (beginning of new phase I trials)?

CT

## Medical Descriptors:

\*solid tumor: DT, drug therapy  
drug industry  
cancer chemotherapy  
drug efficacy  
drug safety  
advanced cancer  
drug activity  
drug structure  
cancer growth  
drug potentiation  
treatment outcome  
side effect: SI, side effect  
tendinitis: SI, side effect  
arthralgia: SI, side effect  
muscle rigidity: SI, side effect  
edema: SI, side effect  
skin discoloration: SI, side effect  
thrombocytopenia: SI, side effect  
enzyme defect: SI, side effect  
nausea: SI, side effect  
rash: SI, side effect  
thromboembolism: SI, side effect  
myalgia: SI, side effect  
human  
nonhuman  
clinical trial  
phase 1 clinical trial  
phase 3 clinical trial  
review  
priority journal

## Drug Descriptors:

\*matrix metalloproteinase inhibitor: AE, adverse drug reaction  
\*matrix metalloproteinase inhibitor: CT, clinical trial  
\*matrix metalloproteinase inhibitor: CB, drug combination  
\*matrix metalloproteinase inhibitor: IT, drug interaction  
\*matrix metalloproteinase inhibitor: DT, drug therapy  
\*matrix metalloproteinase inhibitor: PK, pharmacokinetics  
\*matrix metalloproteinase inhibitor: PD, pharmacology  
\*matrix metalloproteinase inhibitor: IP, intraperitoneal drug administration  
\*matrix metalloproteinase inhibitor: PL, intrapleural drug administration  
\*matrix metalloproteinase inhibitor: PO, oral drug administration

matrix metalloproteinase: EC, endogenous compound  
batimastat: AE, adverse drug reaction  
batimastat: CT, clinical trial  
batimastat: DT, drug therapy  
batimastat: PD, pharmacology  
batimastat: IP, intraperitoneal drug administration  
batimastat: PL, intrapleural drug administration  
tanomastat: CT, clinical trial  
tanomastat: CB, drug combination  
tanomastat: CM, drug comparison  
tanomastat: IT, drug interaction  
tanomastat: DT, drug therapy  
tanomastat: PD, pharmacology  
tanomastat: PO, oral drug administration  
prinomastat: CT, clinical trial  
prinomastat: CB, drug combination  
prinomastat: IT, drug interaction  
prinomastat: DT, drug therapy  
prinomastat: PD, pharmacology  
prinomastat: IP, intraperitoneal drug administration  
prinomastat: PO, oral drug administration  
marimastat: AE, adverse drug reaction  
marimastat: CT, clinical trial  
marimastat: CB, drug combination  
marimastat: CM, drug comparison  
marimastat: CR, drug concentration  
marimastat: DO, drug dose  
marimastat: IT, drug interaction  
marimastat: DT, drug therapy  
marimastat: PK, pharmacokinetics  
marimastat: PD, pharmacology  
marimastat: PO, oral drug administration  
marimastat: SC, subcutaneous drug administration  
cytotoxic agent: CT, clinical trial  
cytotoxic agent: CB, drug combination  
cytotoxic agent: IT, drug interaction  
cytotoxic agent: DT, drug therapy  
cytotoxic agent: PD, pharmacology  
cisplatin: CB, drug combination  
cisplatin: IT, drug interaction  
cisplatin: DT, drug therapy  
cisplatin: PD, pharmacology  
doxorubicin: CB, drug combination  
doxorubicin: IT, drug interaction  
doxorubicin: DT, drug therapy  
doxorubicin: PD, pharmacology  
n1 (1 carbamoyl 2,2 dimethylpropyl) 2 [3 (4 chlorophenyl)propyl] n4  
hydroxybutanediamide: CB, drug combination  
n1 (1 carbamoyl 2,2 dimethylpropyl) 2 [3 (4 chlorophenyl)propyl] n4  
hydroxybutanediamide: IT, drug interaction  
n1 (1 carbamoyl 2,2 dimethylpropyl) 2 [3 (4 chlorophenyl)propyl] n4  
hydroxybutanediamide: DT, drug therapy  
n1 (1 carbamoyl 2,2 dimethylpropyl) 2 [3 (4 chlorophenyl)propyl] n4  
hydroxybutanediamide: PD, pharmacology  
n1 (1 carbamoyl 2,2 dimethylpropyl) 2 [3 (4 chlorophenyl)propyl] n4  
hydroxybutanediamide: SC, subcutaneous drug administration  
gemcitabine: CT, clinical trial  
gemcitabine: CB, drug combination  
gemcitabine: CM, drug comparison  
gemcitabine: IT, drug interaction

gemcitabine: DT, drug therapy  
gemcitabine: PD, pharmacology  
gemcitabine: IV, intravenous drug administration  
ae 941: CT, clinical trial  
ae 941: DT, drug therapy  
ae 941: PD, pharmacology  
angiogenesis inhibitor: DT, drug therapy  
angiogenesis inhibitor: PD, pharmacology  
tetracycline derivative: DT, drug therapy  
tetracycline derivative: PD, pharmacology  
4 dedimethylaminosacycline: AE, adverse drug reaction  
4 dedimethylaminosacycline: CT, clinical trial  
4 dedimethylaminosacycline: DT, drug therapy  
4 dedimethylaminosacycline: PD, pharmacology  
4 dedimethylaminosacycline: PO, oral drug administration  
d 2163: AE, adverse drug reaction  
d 2163: CT, clinical trial  
d 2163: CB, drug combination  
d 2163: DT, drug therapy  
d 2163: PD, pharmacology  
hydroxamic acid derivative: AE, adverse drug reaction

## CT Drug Descriptors:

hydroxamic acid derivative: CT, clinical trial  
hydroxamic acid derivative: DT, drug therapy  
hydroxamic acid derivative: PD, pharmacology  
hydroxamic acid derivative: PL, intrapleural drug administration  
hydroxamic acid derivative: PO, oral drug administration  
cgs 27023a: AE, adverse drug reaction  
cgs 27023a: CT, clinical trial  
cgs 27023a: DT, drug therapy  
cgs 27023a: PD, pharmacology  
placebo  
temozolomide: AE, adverse drug reaction  
temozolomide: CT, clinical trial  
temozolomide: CB, drug combination  
temozolomide: CM, drug comparison  
temozolomide: IT, drug interaction  
temozolomide: DT, drug therapy  
temozolomide: PD, pharmacology  
fluorouracil: CT, clinical trial  
fluorouracil: CB, drug combination  
fluorouracil: CM, drug comparison  
fluorouracil: IT, drug interaction  
fluorouracil: DT, drug therapy  
fluorouracil: PD, pharmacology  
cipemastat: CT, clinical trial  
cipemastat: DT, drug therapy  
cipemastat: PD, pharmacology  
paclitaxel: CT, clinical trial  
paclitaxel: CB, drug combination  
paclitaxel: DT, drug therapy  
paclitaxel: PD, pharmacology  
carboplatin: CB, drug combination  
carboplatin: DT, drug therapy  
carboplatin: PD, pharmacology  
ilomastat: DT, drug therapy  
ilomastat: PD, pharmacology  
RN (batimastat) 130370-60-4, 130464-84-5; (tanomastat) 179545-76-7,  
179545-77-8; (prinomastat) 192329-42-3, 195008-93-6; (marimastat)  
154039-60-8; (cisplatin) 15663-27-1, 26035-31-4, 96081-74-2; (doxorubicin)

23214-92-8, 25316-40-9; (n1 (1 carbamoyl 2,2 dimethylpropyl) 2 [3 (4 chlorophenyl)propyl] n4 hydroxybutanediamide) 162514-46-7;  
 (gemcitabine) 103882-84-4; (4 dedimethylaminosancycline) 15866-90-7; (d 2163) 191537-76-5; (cgs 27023a) 169799-04-6; (temozolomide) 85622-93-1;  
 (fluorouracil) 51-21-8; (cipemastat) 190648-49-8; (paclitaxel) 33069-62-4;  
 (carboplatin) 41575-94-4; (ilmastat) 142880-36-2

CN (1) Bay 12 9566; (2) Bb 94; (3) Bb 2516; (4) Ag 3340; (5) Bms 275291; (6) Bms 275291; (7) Ro 32 3555; Cgs 27023a; Col 3; Ae 941; Gm 6001  
 CO (1) Bayer; (3) British Biotechnology; (4) Agouron; (5) Bristol; (6) Squibb; (7) Hoffmann La Roche

L51 /ANSWER 27 OF 85 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2002136784 EMBASE

TITLE: Selective requirement for CD40-CD154 in drug-induced type 1 versus type 2 responses to trinitrophenyl-ovalbumin.

AUTHOR: Nierkens S.; Van Helden P.; Bol M.; Bleumink R.; Van Kooten P.; Ramdien-Murli S.; Boon L.; Pieters R.

CORPORATE SOURCE: Dr. S. Nierkens, Department of Immunotoxicology, Institute for Risk Assessment Sci., Utrecht University, P.O. Box 80176, NL 3508 TD Utrecht, Netherlands.

SOURCE: s.nierkens@iras.uu.nl  
 Journal of Immunology, (15 Apr 2002) Vol. 168, No. 8, pp. 3747-3754.

Refs: 49

ISSN: 0022-1767 CODEN: JOIMA3

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 026 Immunology, Serology and Transplantation

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 20020502  
 Last Updated on STN: 20020502

ED Entered STN: 20020502

Last Updated on STN: 20020502

AB CD154 is transiently expressed by activated T cells and interacts with CD40 on B cells, dendritic cells, macrophages, and monocytes. This costimulatory receptor-ligand couple seems decisive in Ag-driven immune responses but may be differentially involved in type 1 vs type 2 responses. We studied the importance of CD40-CD154 in both responses using the reporter Ag popliteal lymph node assay in which selectively acting drugs generate clearly polarized type 1 (streptozotocin) or type 2 (D-penicillamine, diphenylhydantoin) responses to a constant coinjected Ag in the same mouse strain. Treatment of mice with anti-CD154 reduced characteristic immunological parameters in type 2 responses (B and CD4(+) T cell proliferation, IgG1 and IgE Abs, and IL-4 secretion) and only slightly affected the type 1 response (small decrease in IFN- $\gamma$  production, influx of CD11c(+) and F4/80(+) cells, and prevention of architectural disruption of the lymph node, but no effect on IgG2a Ab and TNF- $\alpha$  secretion or B and CD4(+) T cell proliferation). The findings indicate that the CD40-CD154 costimulatory interaction is a prerequisite in drug-induced type 2 responses and is only marginally involved in type 1 responses. The observed expression patterns of CD80 and CD86 on different APC (B cells in type 2 and dendritic cells in type 1) may be responsible for this discrepancy.

CT Medical Descriptors:

- \*immune response
- antigen expression
- T lymphocyte activation

B lymphocyte  
cell interaction  
cytokine release  
lymphocyte proliferation  
cytokine production  
lymph node  
antigen presenting cell  
dendritic cell  
nonhuman  
female  
mouse  
controlled study  
animal cell  
article  
priority journal  
Drug Descriptors:  
\*CD40 antigen: EC, endogenous compound  
\*CD40 ligand: EC, endogenous compound  
    \*trinitrophenyl  
\*ovalbumin  
streptozocin  
penicillamine  
    phenytoin  
CD40 ligand monoclonal antibody  
immunoglobulin G1: EC, endogenous compound  
immunoglobulin E antibody: EC, endogenous compound  
immunoglobulin G antibody: EC, endogenous compound  
interleukin 4: EC, endogenous compound  
gamma interferon: EC, endogenous compound  
CD11 antigen: EC, endogenous compound  
    tumor necrosis factor alpha: EC, endogenous compound  
immunoglobulin G2a: EC, endogenous compound  
(CD40 ligand) 226713-27-5; (ovalbumin) 77466-29-6; (streptozocin) 18883-66-4; (penicillamine) 2219-30-9, 52-67-5; (phenytoin) 57-41-0, 630-93-3; (gamma interferon) 82115-62-6

L51 ANSWER 28 OF 85 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2001299910 EMBASE

TITLE: Practical approaches to the matrix metalloproteinase inhibitor Trocade® (Ro 32-3555) and to the TNF- $\alpha$  converting enzyme inhibitor Ro 32-7315.

AUTHOR: Hilpert H.

CORPORATE SOURCE: H. Hilpert, F. Hoffmann-La Roche Ltd, Pharmaceuticals Division, Non-Clin. Development-Process Res., Grenzacherstr. 124, CH-4070 Basel, Switzerland.  
hans.hilpert@roche.com

SOURCE: Tetrahedron, (3 Sep 2001) Vol. 57, No. 36, pp. 7675-7683.  
Refs: 16  
ISSN: 0040-4020 CODEN: TETRAB  
S 0040-4020(01)00720-7

PUBLISHER IDENT.: United Kingdom

COUNTRY: United Kingdom

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 20010913  
Last Updated on STN: 20010913

ED Entered STN: 20010913

AB Last Updated on STN: 20010913  
 Stereoselective methods were found to efficiently prepare 2- and 3-substituted succinates with anti configuration. In the synthesis of Trocade® 1, the **hydantoinmethyl** residue was introduced by alkylation of the non-chelated potassium enolate 19 with the bromomethyl hydantoin 9 to give a 92:8 mixture favouring the 2,3-anti configurated succinate 18. The preparation of **TNF-** alpha. converting enzyme (**TACE**) inhibitor 2 was accomplished by a highly stereoselective protonation of the dialkylated enolate 23 using CF(3)CONH(2) affording a 98:2 mixture in favour of the 2,3-anti configurated succinate 24. .COPYRGT. 2001 Elsevier Science Ltd. All right reserved.

CT Medical Descriptors:  
 drug structure  
 reaction analysis  
 stereochemistry  
 drug synthesis  
 alkylation  
 proton transport  
 article  
 priority journal  
 Drug Descriptors:  
 \*matrix metalloproteinase inhibitor: DV, drug development  
 \*cipemastat: DV, drug development  
 \*tumor necrosis factor alpha: DV, drug development  
 \*ro 32 7315: DV, drug development  
 potassium derivative  
 hydantoin derivative  
 unclassified drug

RN (cipemastat) 190648-49-8  
 CN Trocade; Ro 32 3555; Ro 32 7315

L51 ANSWER 29 OF 85 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2001327458 EMBASE  
 TITLE: Design and synthesis of **matrix metalloproteinase** inhibitors guided by molecular modeling. Picking the S(1) pocket using conformationally constrained inhibitors.  
 AUTHOR: Hanessian S.; MacKay D.B.; Moitessier N.  
 CORPORATE SOURCE: S. Hanessian, Department of Chemistry, Universite de Montreal, C. P. 6128, Succursale Centre-Ville, Montreal, Que. H3C 3J7, Canada. stephen.hanessian@umontreal.ca  
 SOURCE: Journal of Medicinal Chemistry, (13 Sep 2001) Vol. 44, No. 19, pp. 3074-3082.  
 Refs: 29  
 ISSN: 0022-2623 CODEN: JMCMAR  
 COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article  
 FILE SEGMENT: 030 Pharmacology  
 037 Drug Literature Index  
 LANGUAGE: English  
 SUMMARY LANGUAGE: English  
 ENTRY DATE: Entered STN: 20011018  
 Last Updated on STN: 20011018  
 ED Entered STN: 20011018  
 Last Updated on STN: 20011018  
 AB Conformationally constrained **MMP** inhibitors based on a D-proline scaffold were designed using AutoDock as a modeling program. Thus a family of D-proline **hydroxamic acids**, having differentiated

functionality at the site of binding to the S(1) pocket, was synthesized. Biological evaluation showed low nanomolar activity and modest selectivity toward different MMP subclasses, delineating the importance of binding to the S(1) pocket for both activity and selectivity.

## CT Medical Descriptors:

drug design  
drug synthesis  
molecular model  
drug conformation  
binding site  
enzyme inhibition  
structure activity relation  
IC 50  
drug potency  
hydrophobicity  
article

## Drug Descriptors:

\*matrix metalloproteinase inhibitor: AN, drug analysis  
\*matrix metalloproteinase inhibitor: DV, drug development  
\*matrix metalloproteinase inhibitor: PD, pharmacology  
\*hydroxamic acid derivative: AN, drug analysis  
\*hydroxamic acid derivative: DV, drug development  
\*hydroxamic acid derivative: PD, pharmacology  
proline

**matrix metalloproteinase**

batimastat

**cipemastat**

cgs 27023a

RN (proline) 147-85-3, 7005-20-1; (batimastat) 130370-60-4, 130464-84-5;  
(cipemastat) 190648-49-8; (cgs 27023a) 169799-04-6

CO Bachem (Switzerland)

L51 ANSWER 30 OF 85 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2001327457 EMBASE

TITLE: N-aryl sulfonyl homocysteine hydroxamate  
inhibitors of **matrix metalloproteinases**  
: Further probing of the S(1), S(1)', and S(2)' pockets.

AUTHOR: Hanessian S.; Moitessier N.; Gauchet C.; Viau M.

CORPORATE SOURCE: S. Hanessian, Department of Chemistry, Universite de  
Montreal, C.P. 6128, Succursale Centre-Ville, Montreal,  
Que. H3C 3J7, Canada. stephen.hanessian@umontreal.ca

SOURCE: Journal of Medicinal Chemistry, (13 Sep 2001) Vol. 44, No.  
19, pp. 3066-3073.

Refs: 40

ISSN: 0022-2623 CODEN: JMCMAR

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 030 Pharmacology

037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 20011018

Last Updated on STN: 20011018

ED Entered STN: 20011018

Last Updated on STN: 20011018

AB A series of N-arylsulfonyl S-alkyl homocysteine hydroxamic acids  
were synthesized with variations in three subsites corresponding to P(1),  
P(1)', and P(2)'. Enzyme assays with a variety of MMPs revealed  
activity at the low nanomolar level.

CT Medical Descriptors:  
 drug synthesis  
 enzyme assay  
 enzyme inhibition  
 enzyme activity  
 structure activity relation  
 chemical modification  
 molecular model  
 IC 50  
 article  
 Drug Descriptors:  
 \*homocysteine  
 \*hydroxamic acid derivative: AN, drug analysis  
 \*hydroxamic acid derivative: DV, drug development  
 \*hydroxamic acid derivative: PD, pharmacology  
 \*sulfonyl homocysteine hydroxamate derivative: AN, drug analysis  
 \*sulfonyl homocysteine hydroxamate derivative: DV, drug development  
 \*sulfonyl homocysteine hydroxamate derivative: PD, pharmacology  
 \*matrix metalloproteinase inhibitor: AN, drug analysis  
 \*matrix metalloproteinase inhibitor: DV, drug development  
 \*matrix metalloproteinase inhibitor: PD, pharmacology  
 stromelysin  
 marimastat  
 cipemastat  
 cgs 27023a  
 prinomastat  
 gelatinase A  
 gelatinase B  
 interstitial collagenase  
 collagenase 3  
 unclassified drug  
 RN (homocysteine) 454-28-4, 6027-13-0; (stromelysin) 79955-99-0; (marimastat) 154039-60-8; (cipemastat) 190648-49-8; (cgs 27023a) 169799-04-6; (prinomastat) 192329-42-3, 195008-93-6; (gelatinase A) 146480-35-5; (gelatinase B) 146480-36-6; (collagenase 3) 175449-82-8  
 CN (1) Ro 32 3555; (2) Cgs 27023a; (3) Cgs 27023a; (4) Ag 3340  
 CO (1) Hoffmann La Roche; (2) Ciba Geigy; (3) Novartis; (4) Agouron; British Biotechnology

L51 ANSWER 31 OF 85 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2001270928 EMBASE  
 TITLE: Biaryl ether retrohydroxamates as potent, long-lived, orally bioavailable MMP inhibitors.  
 AUTHOR: Michaelides M.R.; Dellaria J.F.; Gong J.; Holms J.H.; Bouska J.J.; Stacey J.; Wada C.K.; Heyman H.R.; Curtin M.L.; Guo Y.; Goodfellow C.L.; Elmore I.B.; Albert D.H.; Magoc T.J.; Marcotte P.A.; Morgan D.W.; Davidsen S.K.  
 CORPORATE SOURCE: M.R. Michaelides, Cancer Research Area, Abbott Laboratories, Dept. 47J, 100 Abbott Park Road, Abbott Park, IL 60064, United States. michael.michaelides@abbott.com  
 SOURCE: Bioorganic and Medicinal Chemistry Letters, (18 Jun 2001) Vol. 11, No. 12, pp. 1553-1556.  
 Refs: 10  
 ISSN: 0960-894X CODEN: BMCLE8  
 PUBLISHER IDENT.: S 0960-894X(01)00031-2  
 COUNTRY: United Kingdom  
 DOCUMENT TYPE: Journal; Article  
 FILE SEGMENT: 016 Cancer  
 030 Pharmacology

## 037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 20010816

Last Updated on STN: 20010816

ED Entered STN: 20010816

Last Updated on STN: 20010816

AB A novel series of biaryl ether reverse hydroxamate MMP inhibitors has been developed. These compounds are potent MMP-2 inhibitors with limited activity against MMP-1. Select members of this series exhibit excellent pharmacokinetic properties with long elimination half-lives (7 h) and high oral bioavailability (100%).  
.COPYRGT. 2001 Elsevier Science Ltd. All rights reserved.

CT Medical Descriptors:

drug potency

drug mechanism

drug half life

drug bioavailability

drug structure

drug synthesis

reaction analysis

IC 50

enzyme inhibition

stoichiometry

enzyme activity

structure activity relation

monkey

antineoplastic activity

human

nonhuman

rat

clinical trial

animal experiment

controlled study

article

Drug Descriptors:

\*hydroxamic acid derivative: CT, clinical trial

\*hydroxamic acid derivative: AN, drug analysis

\*hydroxamic acid derivative: DV, drug development

\*hydroxamic acid derivative: PK, pharmacokinetics

\*hydroxamic acid derivative: PD, pharmacology

\*hydroxamic acid derivative: IV, intravenous drug administration

\*hydroxamic acid derivative: PO, oral drug administration

\*matrix metalloproteinase inhibitor: CT, clinical trial

\*matrix metalloproteinase inhibitor: AN, drug analysis

\*matrix metalloproteinase inhibitor: DV, drug development

\*matrix metalloproteinase inhibitor: PK, pharmacokinetics

\*matrix metalloproteinase inhibitor: PD, pharmacology

\*matrix metalloproteinase inhibitor: IV, intravenous drug

administration

\*matrix metalloproteinase inhibitor: PO, oral drug administration

\*ether retrohydroxamate derivative: CT, clinical trial

\*ether retrohydroxamate derivative: AN, drug analysis

\*ether retrohydroxamate derivative: DV, drug development

\*ether retrohydroxamate derivative: PK, pharmacokinetics

\*ether retrohydroxamate derivative: PD, pharmacology

\*ether retrohydroxamate derivative: IV, intravenous drug administration

\*ether retrohydroxamate derivative: PO, oral drug administration

ether hydroxamate derivative: CT, clinical trial

ether hydroxamate derivative: AN, drug analysis

ether hydroxamate derivative: DV, drug development  
ether hydroxamate derivative: PK, pharmacokinetics  
ether hydroxamate derivative: PD, pharmacology  
ether hydroxamate derivative: PO, oral drug administration  
    hydantoin derivative: CT, clinical trial  
    hydantoin derivative: CM, drug comparison  
    hydantoin derivative: DV, drug development  
    hydantoin derivative: PK, pharmacokinetics  
    hydantoin derivative: PD, pharmacology  
    hydantoin derivative: PO, oral drug administration  
antineoplastic agent: CT, clinical trial  
antineoplastic agent: AN, drug analysis  
antineoplastic agent: CM, drug comparison  
antineoplastic agent: DV, drug development  
antineoplastic agent: PK, pharmacokinetics  
antineoplastic agent: PD, pharmacology  
antineoplastic agent: IV, intravenous drug administration  
antineoplastic agent: PO, oral drug administration  
acetic acid derivative: CM, drug comparison  
acetic acid derivative: PK, pharmacokinetics  
acetic acid derivative: PD, pharmacology  
acetic acid derivative: IV, intravenous drug administration  
succinimide derivative: CM, drug comparison  
succinimide derivative: PK, pharmacokinetics  
succinimide derivative: PD, pharmacology  
succinimide derivative: IV, intravenous drug administration  
phthalimide derivative: CM, drug comparison  
phthalimide derivative: PK, pharmacokinetics  
phthalimide derivative: PD, pharmacology  
phthalimide derivative: IV, intravenous drug administration  
pyridazinone derivative: CM, drug comparison  
pyridazinone derivative: PK, pharmacokinetics  
pyridazinone derivative: PD, pharmacology  
pyridazinone derivative: IV, intravenous drug administration

    cipemastat: CT, clinical trial  
    cipemastat: CM, drug comparison  
    cipemastat: DV, drug development  
    cipemastat: PK, pharmacokinetics  
    cipemastat: PD, pharmacology  
    cipemastat: PO, oral drug administration  
d 2163: CT, clinical trial  
d 2163: CM, drug comparison  
d 2163: DV, drug development  
d 2163: PK, pharmacokinetics  
d 2163: PD, pharmacology  
d 2163: PO, oral drug administration  
drug metabolite  
unclassified drug

RN (cipemastat) 190648-49-8; (d 2163) 191537-76-5  
CN D 2163; Ro 323555

L51 ANSWER 32 OF 85 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2001068613 EMBASE  
TITLE: Novel spirohydantoins of D-allose and D-ribose derived from glyco- $\alpha$ -aminonitriles.  
AUTHOR: Postel D.; Nguyen Van Nhien A.; Villa P.; Ronco G.  
CORPORATE SOURCE: D. Postel, Laboratoire des Glucides, Universite de Picardie-Jules Verne, 33 rue Saint Leu, 80039 Amiens, France. denis.postel@sc.u-picardie.fr

SOURCE: Tetrahedron Letters, (19 Feb 2001) Vol. 42, No. 8, pp. 1499-1502.  
 Refs: 12  
 ISSN: 0040-4039 CODEN: TELEAY

PUBLISHER IDENT.: S 0040-4039(00)02294-2

COUNTRY: United Kingdom

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 029 Clinical Biochemistry

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 20010316  
 Last Updated on STN: 20010316

ED Entered STN: 20010316  
 Last Updated on STN: 20010316

AB The synthesis of 3-spirohydantoin derivatives of D-allose and D-ribose is reported. The key step is the stereoselective conversion of glyco- $\alpha$ -aminonitriles from ulose derivatives of D-glucose and D-xylose using titanium(IV) isopropoxide as a mild and efficient catalyst. Cyclisation of the glyco- $\alpha$ -aminonitriles give the target spirohydantoins. .COPYRGT. 2001 Elsevier Science Ltd.

CT Medical Descriptors:  
 \*cyclization  
 synthesis  
 catalyst  
 precursor  
 oxidation  
 reaction analysis  
 decarboxylation  
 article  
 Drug Descriptors:  
 \*allose  
 \*ribose  
 \*nitrile  
 \*glyco alpha aminonitrile  
 \*hydantoin derivative  
 \*3 spirohydantoin  
 glucose  
 xylose  
 titanium derivative  
 titanium 4 isopropoxide  
 unclassified drug

RN (allose) 6038-51-3; (ribose) 34466-20-1, 50-69-1, 93781-19-2; (glucose) 50-99-7, 84778-64-3; (xylose) 25990-60-7, 58-86-6

L51 ANSWER 33 OF 85 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2001202807 EMBASE

TITLE: Induction of tumour cell apoptosis by matrix metalloproteinase inhibitors: New tricks from a (not so) old drug.

AUTHOR: Mitsiades N.; Poulaki V.; Mitsiades C.S.; Anderson K.C.

Corporate SOURCE: K.C. Anderson, Department of Adult Oncology, Dana-Farber Cancer Institute, 44 Binney Street, Boston, MA 02115, United States

SOURCE: Expert Opinion on Investigational Drugs, (2001) Vol. 10, No. 6, pp. 1075-1084.  
 Refs: 86  
 ISSN: 1354-3784 CODEN: EOIDER

COUNTRY: United Kingdom

DOCUMENT TYPE: Journal; General Review  
FILE SEGMENT: 016 Cancer  
029 Clinical Biochemistry  
030 Pharmacology  
037 Drug Literature Index  
038 Adverse Reactions Titles  
LANGUAGE: English  
SUMMARY LANGUAGE: English  
ENTRY DATE: Entered STN: 20010710  
Last Updated on STN: 20010710  
ED Entered STN: 20010710  
Last Updated on STN: 20010710  
AB **Matrix metalloproteinases (MMPs)** regulate the turnover of extracellular matrix (ECM) components and play an important role in embryo development, morphogenesis and tissue remodelling, as well as in tumour invasion and metastasis. Synthetic MMP inhibitors (MMPIs) were designed to prevent tumour cell-induced changes in ECM and thereby achieve antitumour activity. Several MMPIs have entered clinical trials but the preliminary results did not meet the expectations. Recent evidence suggests that **MMPs** may have more diverse roles than originally believed, influencing angiogenesis, cytokine secretion, as well as tumour cell growth and survival. In particular, synthetic MMPIs may directly induce apoptosis of cancer cells via their inhibitory effect on the shedding of Fas Ligand (FasL), a transmembrane member of the TNF superfamily that kills susceptible cells through its receptor, Fas. Several types of cancers have been shown to express FasL and to shed it from their surface as a soluble form, which is significantly less potent in promoting apoptosis. **MMP-7** was recently reported to catalyse this process. Conversely, inhibition of FasL-shedding by a synthetic MMPI results in apoptosis of Fas-sensitive cancer cells. More importantly, DNA-damaging anticancer agents, such as adriamycin, kill cancer cells, at least in part, by upregulating FasL. By inhibiting the proteolytic cleavage of FasL, MMPIs can potentiate the killing effect of traditional chemotherapeutic drugs. These studies therefore demonstrate a direct link between DNA-damaging chemotherapeutic drugs, the apoptosis-inducing Fas/FasL system and the proteolytic activity of **MMPs** and have important therapeutic implications. For example, the proteolytic activity of **MMP-7**, which is broadly expressed in primary and especially metastatic human malignancies, may contribute to tumour resistance to cytotoxic agents; targeting and inactivating **MMP-7** may, therefore, enhance the efficacy of conventional cancer chemotherapy.  
CT Medical Descriptors:  
tumor cell  
apoptosis  
extracellular matrix  
embryo development  
morphogenesis  
cancer invasion  
metastasis  
drug design  
antineoplastic activity  
angiogenesis  
cytokine release  
tumor growth  
cell survival  
cancer cell  
inhibition kinetics  
protein family  
cell killing

drug potency  
enzyme mechanism  
DNA damage  
protein degradation  
drug potentiation  
protein expression  
malignant neoplastic disease: DT, drug therapy  
tumor resistance  
protein targeting  
enzyme inactivation  
drug efficacy  
drug bioavailability  
drug tolerability  
bone marrow suppression: SI, side effect  
immune deficiency: SI, side effect  
gastrointestinal disease: SI, side effect  
volunteer  
musculoskeletal disease: SI, side effect  
drug selectivity  
advanced cancer: DT, drug therapy  
in vitro study  
human  
nonhuman  
mouse  
human experiment  
normal human  
clinical trial  
phase 1 clinical trial  
phase 3 clinical trial  
animal experiment  
animal model  
controlled study  
human cell  
animal cell  
review

## Drug Descriptors:

\*matrix metalloproteinase inhibitor: CT, clinical trial  
\*matrix metalloproteinase inhibitor: DV, drug development  
\*matrix metalloproteinase inhibitor: IT, drug interaction  
\*matrix metalloproteinase inhibitor: DT, drug therapy  
\*matrix metalloproteinase inhibitor: PD, pharmacology  
matrix metalloproteinase: EC, endogenous compound  
cytokine: EC, endogenous compound  
FAS ligand: EC, endogenous compound  
membrane protein: EC, endogenous compound  
tumor necrosis factor: EC, endogenous compound  
Fas antigen: EC, endogenous compound  
matrilysin: EC, endogenous compound  
antineoplastic agent: IT, drug interaction  
antineoplastic agent: DT, drug therapy  
antineoplastic agent: PD, pharmacology  
doxorubicin: DT, drug therapy  
doxorubicin: PD, pharmacology  
cytotoxic agent: PD, pharmacology  
interstitial collagenase: EC, endogenous compound  
batimastat: CT, clinical trial  
batimastat: DV, drug development  
batimastat: DT, drug therapy  
batimastat: PK, pharmacokinetics  
batimastat: PD, pharmacology

marimastat: CT, clinical trial  
marimastat: DV, drug development  
marimastat: DT, drug therapy  
marimastat: PD, pharmacology  
prinomastat: AE, adverse drug reaction  
prinomastat: CT, clinical trial  
prinomastat: DV, drug development  
prinomastat: DT, drug therapy  
prinomastat: PD, pharmacology  
4 (4' chlorobiphenyl 4 yl) 4 oxo 2 (phenylthiomethyl)butyric acid:  
AE, adverse drug reaction  
4 (4' chlorobiphenyl 4 yl) 4 oxo 2 (phenylthiomethyl)butyric acid:  
CT, clinical trial  
4 (4' chlorobiphenyl 4 yl) 4 oxo 2 (phenylthiomethyl)butyric acid:  
DV, drug development  
4 (4' chlorobiphenyl 4 yl) 4 oxo 2 (phenylthiomethyl)butyric acid:  
DT, drug therapy  
4 (4' chlorobiphenyl 4 yl) 4 oxo 2 (phenylthiomethyl)butyric acid:  
PD, pharmacology  
cgs 27023a: AE, adverse drug reaction  
cgs 27023a: CT, clinical trial  
cgs 27023a: DV, drug development  
cgs 27023a: DT, drug therapy  
cgs 27023a: PD, pharmacology  
d 2163: AE, adverse drug reaction  
d 2163: CT, clinical trial  
d 2163: DV, drug development  
d 2163: DT, drug therapy  
d 2163: PD, pharmacology  
4 dedimethylaminosancycline: AE, adverse drug reaction  
4 dedimethylaminosancycline: CT, clinical trial  
4 dedimethylaminosancycline: DV, drug development  
4 dedimethylaminosancycline: DT, drug therapy  
4 dedimethylaminosancycline: PD, pharmacology  
nerve growth factor receptor: EC, endogenous compound  
caspase 8: EC, endogenous compound  
tumor necrosis factor alpha: EC, endogenous compound  
tumor necrosis factor alpha converting enzyme: PD, pharmacology  
solimastat: CT, clinical trial  
solimastat: DV, drug development  
solimastat: DT, drug therapy  
solimastat: PD, pharmacology  
cipemastat: CT, clinical trial  
cipemastat: DV, drug development  
cipemastat: DT, drug therapy  
**CT** Drug Descriptors:  
cipemastat: PD, pharmacology  
4 [[[4 (4 chlorophenoxy)phenyl]sulfonyl]methyl]tetrahydro 2h pyran 4  
carbohydroxamic acid: CT, clinical trial  
4 [[[4 (4 chlorophenoxy)phenyl]sulfonyl]methyl]tetrahydro 2h pyran 4  
carbohydroxamic acid: DV, drug development  
4 [[[4 (4 chlorophenoxy)phenyl]sulfonyl]methyl]tetrahydro 2h pyran 4  
carbohydroxamic acid: DT, drug therapy  
4 [[[4 (4 chlorophenoxy)phenyl]sulfonyl]methyl]tetrahydro 2h pyran 4  
carbohydroxamic acid: PD, pharmacology  
gelatinase A: EC, endogenous compound  
stromelysin: EC, endogenous compound  
gelatinase B: EC, endogenous compound  
unindexed drug  
**RN** (matrilysin) 141256-52-2; (doxorubicin) 23214-92-8, 25316-40-9;

(batimastat) 130370-60-4, 130464-84-5; (marimastat) 154039-60-8;  
 (prinomastat) 192329-42-3, 195008-93-6; (4 (4' chlorobiphenyl 4  
 yl) 4 oxo 2 (phenylthiomethyl)butyric acid) 179545-76-7,  
 179545-77-8; (cgs 27023a) 169799-04-6; (d 2163) 191537-76-5; (4  
 dedimethylaminosacycline) 15866-90-7; (tumor necrosis  
 factor alpha converting enzyme) 151769-16-3;  
 (cipemastat) 190648-49-8; (4 [[4 (4 chlorophenoxy)phenyl  
 ]sulfonyl]methyl]tetrahydro 2h pyran 4 carbohydroxamic acid) 193022-04-7;  
 (gelatinase A) 146480-35-5; (stromelysin) 79955-99-0; (gelatinase B)  
 146480-36-6

CN (1) Ag 3340; (2) Ag 3340; (3) Bay 129566; (4) Cgs 27023a; (5) Bms 275291;  
 (6) Bms 275291; (7) Metastat; Bb 94; Bb 2516; Ro 32 3555; Rs 130830  
 CO (1) Agouron; (2) Pfizer; (3) Bayer; (4) Novartis; (5) Celltech; (6) Bms;  
 (7) Collagenex

L51 ANSWER 34 OF 85 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2002038795 EMBASE

TITLE: Metalloproteases and inhibitors in arthritic diseases.

AUTHOR: Martel-Pelletier J.; Welsch D.J.; Pelletier J.-P.

CORPORATE SOURCE: Prof. Dr. J. Martel-Pelletier, Osteoarthritis Research Unit, Hopital Notre-Dame, Ctr. Hosp. de l'Univ. de Montreal, 1560 rue Sherbrooke Est, Montreal, Que., Canada Bailliere's Best Practice and Research in Clinical Rheumatology, (2001) Vol. 15, No. 5, pp. 805-829.

Refs: 65

ISSN: 1521-6942 CODEN: BBPRFF

COUNTRY: United Kingdom

DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 031 Arthritis and Rheumatism

030 Pharmacology

038 Adverse Reactions Titles

029 Clinical Biochemistry

005 General Pathology and Pathological Anatomy

037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 20020207

Last Updated on STN: 20020207

ED Entered STN: 20020207

Last Updated on STN: 20020207

AB Controlling degradation of the extracellular matrix is crucial in arthritic diseases such as osteoarthritis (OA) and rheumatoid arthritis (RA), as conventional treatments do not positively affect the structural properties of the articular tissues. Metalloproteases, a family of zinc-dependent enzymes, and more specifically the **matrix metalloproteases (MMPs)**, play a premier role in joint articular tissue degeneration. Additional enzymes of the metalloprotease family, such as the membrane-type metalloproteases (MT-MMPs) and the adamalysins that include the ADAMs and the ADAMTS families, have also been found to be involved in these disease processes. At present, therapeutic intervention based on the inhibition of metalloproteases, and more particularly of the **MMPs**, is under intensive investigation, and several **MMP** inhibitors are in clinical development.

Currently, **MMP** inhibitors are exemplified by several chemical classes: hydroxamic acids, carboxylic acids and thiols. One key issue in the clinical development of **MMP** inhibitors relates to whether broad-spectrum inhibitors active against a range of different enzymes or selective inhibitors targeted against a single enzyme or particular subset of the **MMPs** represents the optimal strategy.

In this chapter, we address the different metalloprotease enzymes and sub-families and their implication in arthritic diseases. Furthermore, we assess physiological and chemical metalloprotease inhibitors, and for the latter, the current inhibitory classes of compounds being studied.

CT Medical Descriptors:

\*arthritis: DT, drug therapy  
\*arthritis: ET, etiology  
\*arthritis: DI, diagnosis  
human  
clinical trial  
nonhuman  
degradation  
extracellular matrix  
osteoarthritis: DT, drug therapy  
osteoarthritis: ET, etiology  
osteoarthritis: DI, diagnosis  
rheumatoid arthritis: DT, drug therapy  
rheumatoid arthritis: ET, etiology  
rheumatoid arthritis: DI, diagnosis  
tissue degeneration: ET, etiology  
enzyme inhibition  
physiology  
enzyme synthesis  
enzyme activation  
drug bioavailability  
drug identification  
structure activity relation  
musculoskeletal disease: SI, side effect  
drug synthesis  
drug design  
dose response  
rash: SI, side effect  
nuclear magnetic resonance imaging  
articular cartilage  
transcription regulation  
review  
priority journal

Drug Descriptors:

\*metalloproteinase: EC, endogenous compound  
\*metalloproteinase inhibitor: PD, pharmacology  
\*metalloproteinase inhibitor: DT, drug therapy  
\*metalloproteinase inhibitor: DV, drug development  
\*metalloproteinase inhibitor: AN, drug analysis  
\*metalloproteinase inhibitor: PK, pharmacokinetics  
\*metalloproteinase inhibitor: PO, oral drug administration  
\*metalloproteinase inhibitor: AE, adverse drug reaction  
\*metalloproteinase inhibitor: DO, drug dose  
\*metalloproteinase inhibitor: CT, clinical trial  
\*metalloproteinase inhibitor: CM, drug comparison  
\*metalloproteinase inhibitor: IV, intravenous drug administration  
zinc: EC, endogenous compound  
matrix metalloproteinase: EC, endogenous compound  
matrix metalloproteinase 14: EC, endogenous compound  
hydroxamic acid: PD, pharmacology  
carboxylic acid: PD, pharmacology  
thiol derivative: PD, pharmacology  
thiol derivative: CM, drug comparison  
tissue inhibitor of metalloproteinase: PD, pharmacology  
tissue inhibitor of metalloproteinase: DT, drug therapy  
tissue inhibitor of metalloproteinase: PO, oral drug administration

tissue inhibitor of metalloproteinase: PK, pharmacokinetics  
tetracycline derivative: PD, pharmacology  
tetracycline derivative: DT, drug therapy  
tetracycline derivative: IV, intravenous drug administration  
antibiotic agent: PD, pharmacology  
antibiotic agent: DT, drug therapy  
antibiotic agent: CT, clinical trial  
antibiotic agent: IV, intravenous drug administration  
bryostatin: PD, pharmacology  
bisphosphonic acid derivative: PD, pharmacology  
doxycycline: PD, pharmacology  
doxycycline: IV, intravenous drug administration  
doxycycline: DT, drug therapy  
**tumor necrosis factor alpha converting enzyme: EC, endogenous compound**  
cyclooxygenase 2 inhibitor: DT, drug therapy  
cyclooxygenase 2 inhibitor: PD, pharmacology  
nonsteroid antiinflammatory agent: DT, drug therapy  
nonsteroid antiinflammatory agent: PD, pharmacology  
sc 44463: AN, drug analysis  
sc 44463: PD, pharmacology  
sc 44463: PK, pharmacokinetics  
sc 44463: PO, oral drug administration  
sc 44463: AE, adverse drug reaction  
sc 44463: DT, drug therapy  
batimastat: AN, drug analysis  
batimastat: PD, pharmacology  
batimastat: PK, pharmacokinetics  
batimastat: PO, oral drug administration  
batimastat: AE, adverse drug reaction  
batimastat: DT, drug therapy  
ilomastat: AN, drug analysis  
ilomastat: PD, pharmacology  
ilomastat: PK, pharmacokinetics  
ilomastat: PO, oral drug administration  
ilomastat: AE, adverse drug reaction  
ilomastat: DT, drug therapy  
marimastat: PD, pharmacology  
marimastat: PO, oral drug administration  
marimastat: PK, pharmacokinetics  
marimastat: AE, adverse drug reaction  
marimastat: AN, drug analysis  
marimastat: DO, drug dose  
marimastat: CT, clinical trial  
marimastat: DT, drug therapy  
prinomastat: PD, pharmacology  
prinomastat: PO, oral drug administration  
prinomastat: AN, drug analysis  
prinomastat: DT, drug therapy  
d 2163: PD, pharmacology  
d 2163: DT, drug therapy  
    **cipemastat: PD, pharmacology**  
    **cipemastat: CT, clinical trial**  
    **cipemastat: DT, drug therapy**  
cgs 27023a: PD, pharmacology  
cgs 27023a: PO, oral drug administration  
cgs 27023a: AN, drug analysis  
cgs 27023a: DT, drug therapy  
    **4 [[4 (4 chlorophenoxy)phenyl]sulfonyl]methyl]tetrahydro 2h pyran 4 carbohydroxamic acid: PD, pharmacology**

4 [[[4 (4 chlorophenoxy)phenyl]sulfonyl]methyl]tetrahydro 2h pyran 4  
 carbohydroxamic acid: CT, clinical trial  
 4 [[[4 (4 chlorophenoxy)phenyl]sulfonyl]methyl]tetrahydro 2h pyran 4  
 carbohydroxamic acid: CB, drug combination  
 4 [[[4 (4 chlorophenoxy)phenyl]sulfonyl]methyl]tetrahydro 2h pyran 4  
 carbohydroxamic acid: DT, drug therapy  
 bay 12 9556: PD, pharmacology  
 CT Drug Descriptors:  
 bay 12 9556: DT, drug therapy  
 rs 102481: PD, pharmacology  
 rs 102481: DT, drug therapy  
 minocycline: PD, pharmacology  
 minocycline: DT, drug therapy  
 unindexed drug  
 unclassified drug  
 RN (metalloproteinase) 81669-70-7; (zinc) 7440-66-6; (thiol derivative)  
 13940-21-1; (tissue inhibitor of metalloproteinase) 97837-28-0;  
 (doxycycline) 10592-13-9, 17086-28-1, 564-25-0; (**tumor**  
**necrosis factor alpha converting enzyme**)  
 151769-16-3; (batimastat) 130370-60-4, 130464-84-5; (ilomastat)  
 142880-36-2; (marimastat) 154039-60-8; (prinomastat) 192329-42-3,  
 195008-93-6; (d 2163) 191537-76-5; (cipemastat) 190648-49-8; (cgs 27023a)  
 169799-04-6; (4 [[[4 (4 chlorophenoxy)phenyl]  
 ]sulfonyl]methyl]tetrahydro 2h pyran 4 carbohydroxamic acid) 193022-04-7;  
 (minocycline) 10118-90-8, 11006-27-2, 13614-98-7  
 CN (1) Trocade; (2) Ro 32 3555; Bb 94; Gm 6001; Sc 44463; Bb 2516; Ag 3340; D  
 2163; Bms 275291; Cgs 27023a; Rs 102481; Bay 12 9556; Rs 130830  
 CO (2) Hoffmann La Roche  
  
 L51 ANSWER 35 OF 85 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights  
 reserved on STN  
 ACCESSION NUMBER: 2001050554 EMBASE  
 TITLE: General synthesis of  $\alpha$ -substituted 3-bisaryloxy  
 propionic acid derivatives as specific **MMP**  
 inhibitors.  
 AUTHOR: Chollet A.-M.; Le Diguarher T.; Murray L.; Bertrand M.;  
 Tucker G.C.; Sabatini M.; Pierre A.; Atassi G.; Bonnet J.;  
 Casara P.  
 CORPORATE SOURCE: P. Casara, Institut de Recherches Servier, 125 chemin de  
 Ronde, 78290 Croissy sur Seine, France.  
 patrick.casara@fr.netgrs.com  
 SOURCE: Bioorganic and Medicinal Chemistry Letters, (12 Feb 2001)  
 Vol. 11, No. 3, pp. 295-299.  
 Refs: 45  
 ISSN: 0960-894X CODEN: BMCL8  
 PUBLISHER IDENT.: S 0960-894X(00)00646-6  
 COUNTRY: United Kingdom  
 DOCUMENT TYPE: Journal; Article  
 FILE SEGMENT: 030 Pharmacology  
 037 Drug Literature Index  
 LANGUAGE: English  
 SUMMARY LANGUAGE: English  
 ENTRY DATE: Entered STN: 20010322  
 Last Updated on STN: 20010322  
 ED Entered STN: 20010322  
 Last Updated on STN: 20010322  
 AB Modulations of  $\alpha$  and aryl substitutions on 3-aryloxy propionic acid  
 hydroxamates led to novel and potent inhibitors of **MMP**  
 -2, 3, 9 and 13, and selectivity versus **MMP-1**. .COPYRGT. 2001  
 Elsevier Science Ltd.

## CT Medical Descriptors:

\*drug synthesis  
enzyme inhibition  
drug structure  
human  
controlled study  
human cell  
article

## Drug Descriptors:

\*matrix metalloproteinase inhibitor: AN, drug analysis  
\*matrix metalloproteinase inhibitor: DV, drug development  
\*propionic acid derivative: AN, drug analysis  
\*propionic acid derivative: DV, drug development  
gelatinase A  
gelatinase B

matrix metalloproteinase  
interstitial collagenase  
cipemastat  
marimastat  
prinomastat  
cgs 27023a

RN (gelatinase A) 146480-35-5; (gelatinase B) 146480-36-6; (cipemastat) 190648-49-8; (marimastat) 154039-60-8; (prinomastat) 192329-42-3, 195008-93-6; (cgs 27023a) 169799-04-6

CN Trocade; Marimastat; Prinomastat; Cgs 27023a

L51 ANSWER 36 OF 85 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2001009796 EMBASE

TITLE: Sulfone reverse hydroxamates as matrix metalloproteinase inhibitors.

SOURCE: Expert Opinion on Therapeutic Patents, (2001) Vol. 11, No. 1, pp. 133-143.

Refs: 30

ISSN: 1354-3776 CODEN: EOTPEG

COUNTRY: United Kingdom

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 016 Cancer  
030 Pharmacology  
031 Arthritis and Rheumatism  
037 Drug Literature Index  
039 Pharmacy

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 20010119

Last Updated on STN: 20010119

ED Entered STN: 20010119

Last Updated on STN: 20010119

AB Abbott has disclosed matrix metalloproteinase

inhibitors (MMPIs) characterised by N-formyl-N-hydroxyamino as the zinc ligand, (4-substituted)phenylsulfonyl as the P1' group fitting the primary specificity pocket of the enzymes and three different spacers (-C-C-C-, -C-C-NR-, -C-C-) connecting these structural elements. As such, the Abbott compounds can be regarded as reverse hydroxamate analogues of the well known classes of  $\gamma$ -sulfone, sulfonamide and  $\beta$ -sulfone hydroxamate MMPIs. Within the  $\beta$ -sulfones, a five-membered saturated heterocyclic ring appended at C-1, especially 1,3-dioxolane, identifies a structural subset claimed as having a unique combination of potency, pharmacokinetics and fewer side effects. A specific compound is singled out, (1S)-1-[(4S)-2,2-dimethyl-1,3-

-dioxolan -4-y1] -2-[[4 -[4-(trifluoromethoxy)phenoxy] -phenyl]sulfonyl] ethyl(N-hydroxy)formamide. Potent inhibition of **MMP-2** (gelatinase A) is documented, especially among the  $\beta$ -sulfones. These compounds are stated to have utility for the treatment of diseases involving tissue degenerative processes, including rheumatoid arthritis, osteoarthritis, osteoporosis, periodontitis, gingivitis, corneal, epidermal or gastric ulceration and tumour growth and metastasis.

## CT Medical Descriptors:

patent  
drug structure  
drug potency  
enzyme inhibition  
tissue degeneration  
rheumatoid arthritis  
osteoarthritis  
osteoporosis  
periodontitis  
gingivitis  
cornea ulcer  
skin ulcer  
stomach ulcer  
tumor growth  
metastasis  
drug activity  
IC 50  
drug bioavailability  
drug synthesis  
chemical reaction  
drug half life  
structure activity relation  
human  
nonhuman  
mouse  
rat  
clinical trial  
animal experiment  
animal model  
controlled study  
article

## Drug Descriptors:

\*matrix metalloproteinase inhibitor: CT, clinical trial  
\*matrix metalloproteinase inhibitor: AN, drug analysis  
\*matrix metalloproteinase inhibitor: CM, drug comparison  
\*matrix metalloproteinase inhibitor: DV, drug development  
\*matrix metalloproteinase inhibitor: PK, pharmacokinetics  
\*matrix metalloproteinase inhibitor: PD, pharmacology  
\*matrix metalloproteinase inhibitor: PO, oral drug administration  
\*matrix metalloproteinase inhibitor: SC, subcutaneous drug  
  
administration  
\*hydroxamic acid derivative: CT, clinical trial  
\*hydroxamic acid derivative: AN, drug analysis  
\*hydroxamic acid derivative: CM, drug comparison  
\*hydroxamic acid derivative: DV, drug development  
\*hydroxamic acid derivative: PK, pharmacokinetics  
\*hydroxamic acid derivative: PD, pharmacology  
\*hydroxamic acid derivative: PO, oral drug administration  
\*hydroxamic acid derivative: SC, subcutaneous drug administration  
\*sulfone derivative: CT, clinical trial  
\*sulfone derivative: AN, drug analysis  
\*sulfone derivative: CM, drug comparison

\*sulfone derivative: DV, drug development  
\*sulfone derivative: PK, pharmacokinetics  
\*sulfone derivative: PD, pharmacology  
\*sulfone derivative: PO, oral drug administration  
\*sulfone derivative: SC, subcutaneous drug administration  
zinc  
ligand  
sulfonamide  
1,3 dioxolane  
1 (2,2 dimethyl 1,3 dioxolan 4 yl) 2 [4 [4  
(trifluoromethoxy)phenoxyphenyl]sulfonyl]ethyl n hydroxyformamide: AN,  
drug analysis  
1 (2,2 dimethyl 1,3 dioxolan 4 yl) 2 [4 [4  
(trifluoromethoxy)phenoxyphenyl]sulfonyl]ethyl n hydroxyformamide: DV,  
drug development  
1 (2,2 dimethyl 1,3 dioxolan 4 yl) 2 [4 [4  
(trifluoromethoxy)phenoxyphenyl]sulfonyl]ethyl n hydroxyformamide: PD,  
pharmacology  
gelatinase A: EC, endogenous compound  
batimastat: CT, clinical trial  
batimastat: AN, drug analysis  
batimastat: PD, pharmacology  
marimastat: CT, clinical trial  
marimastat: AN, drug analysis  
marimastat: CM, drug comparison  
marimastat: PK, pharmacokinetics  
marimastat: PD, pharmacology  
cipemastat: CT, clinical trial  
cipemastat: AN, drug analysis  
cipemastat: PD, pharmacology  
cgs 27023a: CT, clinical trial  
cgs 27023a: AN, drug analysis  
cgs 27023a: CM, drug comparison  
cgs 27023a: PD, pharmacology  
prinomastat: CT, clinical trial  
prinomastat: AN, drug analysis  
prinomastat: CM, drug comparison  
prinomastat: PD, pharmacology  
4 (4' chlorobiphenyl 4 yl) 4 oxo 2 (phenylthiomethyl)butyric acid:  
CT, clinical trial  
4 (4' chlorobiphenyl 4 yl) 4 oxo 2 (phenylthiomethyl)butyric acid:  
AN, drug analysis  
4 (4' chlorobiphenyl 4 yl) 4 oxo 2 (phenylthiomethyl)butyric acid:  
PD, pharmacology  
4 [[[4 (4 chlorophenoxy)phenyl]sulfonyl]methyl]tetrahydro 2h pyran 4  
carbohydroxamic acid: CT, clinical trial  
4 [[[4 (4 chlorophenoxy)phenyl]sulfonyl]methyl]tetrahydro 2h pyran 4  
carbohydroxamic acid: AN, drug analysis  
4 [[[4 (4 chlorophenoxy)phenyl]sulfonyl]methyl]tetrahydro 2h pyran 4  
carbohydroxamic acid: PD, pharmacology  
d 2163: CT, clinical trial  
d 2163: AN, drug analysis  
d 2163: PD, pharmacology  
gw 3333: AN, drug analysis  
gw 3333: PK, pharmacokinetics  
gw 3333: PD, pharmacology  
gw 3333: PO, oral drug administration  
ag 3151: AN, drug analysis  
ag 3151: PD, pharmacology  
interstitial collagenase: EC, endogenous compound

stromelysin: EC, endogenous compound  
 gelatinase B: EC, endogenous compound  
     n [3 (3 phenoxyphenyl)allyl]acetohydroxamic acid: AN, drug  
 analysis  
 bw 218c: AN, drug analysis  
     tumor necrosis factor alpha converting enzyme: EC, endogenous  
 compound  
 gi 179: CM, drug comparison  
 gi 179: PK, pharmacokinetics  
 gi 179: PD, pharmacology  
 gi 179: SC, subcutaneous drug administration  
 gi 184: CM, drug comparison  
 gi 184: PK, pharmacokinetics  
 gi 184: PD, pharmacology  
 unclassified drug  
 ro 1130830  
 RN (zinc) 7440-66-6; (1,3 dioxolane) 646-06-0; (gelatinase A) 146480-35-5;  
     (batimastat) 130370-60-4, 130464-84-5; (marimastat) 154039-60-8;  
     (cipemastat) 190648-49-8; (cgs 27023a) 169799-04-6; (prinomastat)  
     192329-42-3, 195008-93-6; (4 (4' chlorobiphenyl 4 yl) 4 oxo 2 ( phenylthiomethyl)butyric acid) 179545-76-7, 179545-77-8; (4 [[4 (4 chlorophenoxy)phenyl]sulfonyl)methyl]tetrahydro 2h pyran 4 carbohydroxamic acid) 193022-04-7; (d 2163) 191537-76-5; (stromelysin) 79955-99-0; (gelatinase B) 146480-36-6; (n [3 (3 phenoxyphenyl)allyl]acetohydroxamic acid) 106328-57-8; (tumor necrosis factor alpha converting enzyme)  
     151769-16-3  
 CN (1) Ro 323555; (2) Cgs 27023a; (3) Ag 3340; (4) Bay 129566; (5) Ro 1130830; (6) Bms 275291; (7) D 2163; (8) Ag 3151; Gw 3333; Bw 218c; Gi 179; Gi 184  
 CO (2) Novartis; (4) Bayer; (5) Hoffmann La Roche; (7) Chiroscience; (8) Agouron; British Biotechnology; Abbott; Pharmacia; Celltech; Syntex; Glaxo Wellcome; Astra Zeneca; Burroughs Wellcome; Darwin Discovery

L51 ANSWER 37 OF 85 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 93105406 EMBASE  
 DOCUMENT NUMBER: 1993105406  
 TITLE: Cell transforming and oncogenic activity of 2,3,7,8 - tetrachloro - and 2,3,7,8 tetrabromodibenzo-p-dioxin.  
 AUTHOR: Massa T.; Esmaeili A.; Fortmeyer H.; Schlatterer B.; Hagenmaier H.; Chandra P.  
 CORPORATE SOURCE: Molecular Biology (ZBC), University Medical School, Stern-Kai 7, D-6000 Frankfurt 71, Germany  
 SOURCE: Anticancer Research, (1992) Vol. 12, No. 6 B, pp. 2053-2060.  
 ISSN: 0250-7005 CODEN: ANTRD4  
 COUNTRY: Greece  
 DOCUMENT TYPE: Journal; Article  
 FILE SEGMENT: 016 Cancer  
               052 Toxicology  
 LANGUAGE: English  
 SUMMARY LANGUAGE: English  
 ENTRY DATE: Entered STN: 930516  
               Last Updated on STN: 930516  
 ED   Entered STN: 930516  
     Last Updated on STN: 930516  
 AB   We have developed a host-mediated assay system for detection of the transforming activity of chemical carcinogens on peritoneal macrophages, directly, as well as indirectly acting carcinogenic substances

administered intraperitoneally to NMRI mice could be examined in this way. Resident macrophages were recovered by peritoneal lavage from treated and untreated mice and cultured in soft agar. After 5-6 days normal and transformed cells could be distinguished. Statistical analysis comparing cells from 2, 3, 7, 8-tetrachlorodibenzo-dioxin (TCDD)-treated animals with those from control mice proved that the test is positive at least on a significance level of 5%, using the t-test. TCDD revealed a cell-transforming potential that showed a dose-dependent response in this host-mediated assay. The co-carcinogenic activity of TCDD was established in experiments with **diphenylhydantoin**. Low doses of **diphenylhydantoin** which did not exhibit any transforming potential in our system gained a high oncogenic potential by the simultaneous administration of low doses of TCDD, which also had no transforming activity. We have compared the cell transforming potential of TCDD with its bromo analog TBrDD. The cell transforming potential of TCDD is 7 times that of TBrDD. We have succeeded in establishing a permanent cell line from mice treated with TBrDD. The oncogenicity of this cell line was tested in athymic nu/nu mice. Animals treated subcutaneously with these cells (1 x 10<sup>6</sup> cells) developed tumors at the injection site. Using monospecific antibodies to **tumor necrosis factor α (TNF-α)**, we have found that TCDD stimulates the secretion of **TNF-α**. The experimental data reported here lead to the conclusion that TCDD has a carcinogenic as well as a co-carcinogenic activity and has the property to induce **TNF-α**.

## CT Medical Descriptors:

- \*carcinogenicity
- \*cell transformation
- animal cell
- animal experiment
- animal model
- article
- bioassay
- cell line
- chemical carcinogenesis
- controlled study
- immunoassay
- lavage
- mouse
- nonhuman
- peritoneum macrophage
- priority journal
- statistical analysis

## Drug Descriptors:

- \*dioxin: TO, drug toxicity
- 2,3,7,8 tetrachlorodibenzo para dioxin: TO, drug toxicity
- carcinogen: TO, drug toxicity
- phenytoin: TO, drug toxicity**

RN (2,3,7,8 tetrachlorodibenzo para dioxin) 1746-01-6; (phenytoin) 57-41-0,  
630-93-3

L51 ANSWER 38 OF 85 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on  
STN

ACCESSION NUMBER: 2005:364644 BIOSIS

DOCUMENT NUMBER: PREV200510145190

TITLE: **Non-hydroxamate 5-phenylpyrimidine**  
-2,4,6-trione derivatives as selective inhibitors of  
**tumor necrosis factor-alpha**  
**converting enzyme.**

AUTHOR(S): Duan, James J.-W. [Reprint Author]; Lu, Zhonghui;  
Wasserman, Zelda R.; Liu, Rui-Qin; Covington, Maryanne B.;

Decicco, Carl P.  
 CORPORATE SOURCE: Bristol Myers Squibb Pharmaceut Res Inst, Princeton, NJ  
 08543 USA  
 james.duan@bms.com  
 SOURCE: Bioorganic & Medicinal Chemistry Letters, (JUN 15 2005)  
 Vol. 15, No. 12, pp. 2970-2973.  
 CODEN: BMCL8. ISSN: 0960-894X.

DOCUMENT TYPE: Article  
 LANGUAGE: English  
 ENTRY DATE: Entered STN: 14 Sep 2005  
 Last Updated on STN: 14 Sep 2005

ED    Entered STN: 14 Sep 2005  
 Last Updated on STN: 14 Sep 2005

AB    New inhibitors of **tumor necrosis factor-a converting enzyme (TACE)** were discovered with a pyrimidine-2,4,6-trione in place of the commonly used **hydroxamic acid**. These non-**hydroxamate TACE** inhibitors were developed by incorporating a 4-(2methyl-4-quinolinylmethoxy)phenyl group, an optimized **TACE** selective P1' group. Several leads were identified with IC50 values around 100 nM in a porcine **TACE** assay and selective over **MMP-1, -2, -9, -13**, and aggrecanase. (c) 2005 Elsevier Ltd. All rights reserved.

CC    Biochemistry studies - General    10060  
 Enzymes - General and comparative studies: coenzymes    10802  
 Pathology - Therapy    12512  
 Pharmacology - General    22002  
 Pharmacology - Immunological processes and allergy    22018  
 Immunology - General and methods    34502

IT    Major Concepts  
 Pharmacology; Biochemistry and Molecular Biophysics; Immune System  
 (Chemical Coordination and Homeostasis)

IT    Chemicals & Biochemicals  
 matrix metalloproteinase-2 [MMP-2] [EC 3.4.24.24];  
 matrix metalloproteinase-9 [MMP-9] [EC 3.4.24.35]; matrix  
 metalloproteinase-1 [MMP-1] [EC 3.4.24.3]; matrix  
 metalloproteinase-13 [MMP-13]; aggrecanase; tumor necrosis  
 factor-alpha-converting enzyme [TACE]; 5-phenylpyrimidine-2,4,6-  
 trione derivatives: enzyme inhibitor-drug, immunosuppressant-drug,  
 immunologic-drug

ORGN Classifier  
 Suidae    85740  
 Super Taxa  
 Artiodactyla; Mammalia; Vertebrata; Chordata; Animalia  
 Organism Name  
 porcine (common)  
 Taxa Notes  
 Animals, Artiodactyls, Chordates, Mammals, Nonhuman Vertebrates,  
 Nonhuman Mammals, Vertebrates

RN    146480-35-5 (matrix metalloproteinase-2)  
 146480-35-5 (MMP-2)  
 146480-35-5 (EC 3.4.24.24)  
 146480-36-6 (matrix metalloproteinase-9)  
 146480-36-6 (MMP-9)  
 146480-36-6 (EC 3.4.24.35)  
 9001-12-1 (matrix metalloproteinase-1)  
 9001-12-1 (MMP-1)  
 9001-12-1 (EC 3.4.24.3)  
 175449-82-8 (matrix metalloproteinase-13)  
 175449-82-8 (MMP-13)  
 147172-61-0 (aggrecanase)

151769-16-3 (tumor necrosis factor-alpha-converting enzyme)  
151769-16-3 (TACE)

L51 ANSWER 39 OF 85 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 2005:95815 BIOSIS  
 DOCUMENT NUMBER: PREV200500095816  
 TITLE: Synthesis and structure-activity relationships of 4-alkynyloxy phenyl sulfanyl, sulfinyl, and sulfonyl alkyl hydroxamates as tumor necrosis factor-alpha converting enzyme and matrix metalloproteinase inhibitors.

AUTHOR(S): Venkatesan, Aranapakam M. [Reprint Author]; Davis, Jamie M.; Grosu, George T.; Baker, Jannie; Zask, Arie; Levin, Jeremy I.; Ellingboe, John; Skotnicki, Jerauld S.; DiJoseph, John F.; Sung, Amy; Jin, Guixian; Xu, Weixin; McCarthy, Diane Joseph; Barone, Dauphine

CORPORATE SOURCE: Wyeth Ayerst Res, 401 N Middletown Rd, Pearl River, NY, 10965, USA  
 venkata@wyeth.com

SOURCE: Journal of Medicinal Chemistry, (December 2 2004) Vol. 47, No. 25, pp. 6255-6269. print.  
 ISSN: 0022-2623 (ISSN print).

DOCUMENT TYPE: Article  
 LANGUAGE: English  
 ENTRY DATE: Entered STN: 9 Mar 2005  
 Last Updated on STN: 9 Mar 2005

ED Entered STN: 9 Mar 2005  
 Last Updated on STN: 9 Mar 2005

AB A series of 4-alkynyloxy phenyl sulfanyl, sulfinyl and sulfonyl alkyl and piperidine-4-carboxylic acid hydroxamides were synthesized. Their structure-activity relationships, against tumor necrosis factor-alpha (TACE) and matrix metalloproteinase (NIMP) inhibitor activities, are presented by investigating the oxidation state on sulfur and altering the P1' substituent. The sulfonyl derivatives 20-24 carrying a 4-butynyloxy moiety were selective TACE inhibitors over the MMPs tested. The sulfinyl derivatives showed a preference for a specific oxidation on sulfur as in compounds 25-28. The selectivity over MMPs was also demonstrated in the sulfonyl series. The enhanced cellular activity was achieved upon incorporating a butynyloxy substituent in the piperidene series. Compounds 64 and 65 were potent inhibitors of TNF-alpha release in the mouse at 100 mg/kg po.

CC Biochemistry studies - General 10060  
 Biochemistry studies - Proteins, peptides and amino acids 10064

IT Major Concepts  
 Biochemistry and Molecular Biophysics  
 IT Chemicals & Biochemicals  
 4-alkynyloxy phenyl sulfanyl; matrix metalloproteinase inhibitor; piperidine-4-carboxylic acid hydroxamides; sulfinyl; sulfonyl alkyl hydroxamate; sulfur: oxidation state; tumor necrosis factor-alpha

IT Miscellaneous Descriptors  
 structure-activity relationship

ORGN Classifier  
 Hominidae 86215  
 Super Taxa  
 Primates; Mammalia; Vertebrata; Chordata; Animalia

Organism Name  
 human (common)  
 Taxa Notes  
 Animals, Chordates, Humans, Mammals, Primates, Vertebrates  
 RN 13827-32-2 (sulfinyl)  
 7704-34-9 (sulfur)

L51 ANSWER 40 OF 85 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on  
 STN  
 ACCESSION NUMBER: 2004:175141 BIOSIS  
 DOCUMENT NUMBER: PREV200400176872  
 TITLE: Crystal structure of the catalytic domain of human  
**matrix metalloproteinase 10.**  
 AUTHOR(S): Bertini, I. [Reprint Author]; Calderone, V.; Fragai, M.;  
 Luchinat, C.; Mangani, S.; Terni, B.  
 CORPORATE SOURCE: CERM, University of Florence and FiorGen Foundation, Via  
 Sacconi 6, 50019, Sesto Fiorentino, Florence, Italy  
 bertini@cerm.unifi.it  
 SOURCE: Journal of Molecular Biology, (20 February 2004) Vol. 336,  
 No. 3, pp. 707-716. print.  
 ISSN: 0022-2836 (ISSN print).  
 DOCUMENT TYPE: Article  
 LANGUAGE: English  
 ENTRY DATE: Entered STN: 31 Mar 2004  
 Last Updated on STN: 31 Mar 2004  
 ED Entered STN: 31 Mar 2004  
 Last Updated on STN: 31 Mar 2004  
 AB The catalytic domain of **matrix metalloproteinase-10** (**MMP-10**) has been expressed in Escherichia coli and its crystal structure solved at 2.1 ANG resolution. The availability of this structure allowed us to critically examine the small differences existing between the catalytic domains of **MMP-3** and **MMP-10**, which show the highest sequence identity among all **MMPS**. Furthermore, the binding mode of N-isobutyl-N-(4-methoxyphenylsulfonyl)glycyl hydroxamic acid (NNGH), which is one of the most known commercial inhibitors of **MMPS**, is described for the first time.  
 CC Enzymes - General and comparative studies: coenzymes 10802  
 Physiology and biochemistry of bacteria 31000  
 IT Major Concepts  
 Enzymology (Biochemistry and Molecular Biophysics)  
 IT Chemicals & Biochemicals  
 N-isobutyl-N-[4-methoxy-phenylsulfonyl]glycyl hydroxamic acid;  
 matrix metalloproteinase inhibitor; human matrix  
 metalloproteinase 10: catalytic domain crystal structure  
 ORGN Classifier  
 Enterobacteriaceae 06702  
 Super Taxa  
 Facultatively Anaerobic Gram-Negative Rods; Eubacteria; Bacteria;  
 Microorganisms  
 Organism Name  
 Escherichia coli (species)  
 Taxa Notes  
 Bacteria, Eubacteria, Microorganisms  
 ORGN Classifier  
 Hominidae 86215  
 Super Taxa  
 Primates; Mammalia; Vertebrata; Chordata; Animalia  
 Organism Name  
 human (common)

**Taxa Notes**

**Animals, Chordates, Humans, Mammals, Primates, Vertebrates**

L51 ANSWER 41 OF 85 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 2004:420040 BIOSIS  
 DOCUMENT NUMBER: PREV200400420575

TITLE: New radioiodinated carboxylic and hydroxamic matrix metalloproteinase inhibitor tracers as potential tumor imaging agents.

AUTHOR(S): Oltenfreiter, Ruth [Reprint Author]; Staelens, Ludovicus; Lejeune, Annabelle; Dumont, Filip; Franken, Francis; Foidart, Jean-Michel; Slegers, Guido

CORPORATE SOURCE: Dept Radiopharm, State Univ Ghent, Harelbekestr 72, B-9000, Ghent, Belgium  
 ruth.oltenfreiter@rug.ac.be

SOURCE: Nuclear Medicine and Biology, (May 2004) Vol. 31, No. 4, pp. 459-468. print.  
 ISSN: 0969-8051.

DOCUMENT TYPE: Article  
 LANGUAGE: English  
 ENTRY DATE: Entered STN: 3 Nov 2004  
 Last Updated on STN: 3 Nov 2004

ED Entered STN: 3 Nov 2004  
 Last Updated on STN: 3 Nov 2004

AB Several studies have demonstrated a positive correlation between tumor progression and expression of extracellular proteinases such as matrix metalloproteinases (MMPs). MMP -2 and MMP-9 have become attractive targets for cancer research because of their increased expression in human malignant tumor tissues of various organs, providing a target for medical imaging techniques. Radioiodinated carboxylic and hydroxamic MMP inhibitors 2-(4'-(123)iodo-biphenyl-4-sulfonylaminino)-3-(1H-indol-3-yl)-propionic acid (9) and 2-(4'-(123I) iodo-biphenyl-4-sulfonylamino)-3-(1H-indol-3-yl)-propionamide (11) were synthesized by electrophilic aromatic substitution of the tributylstannyl derivatives and resulted in radiochemical yields of 60% +/- 5% (n = 3) and 70% +/- 5% (n = 6), respectively. In vitro zymography and enzyme assays showed high inhibition capacities of the inhibitors on gelatinases. In vivo biodistribution showed no long-term accumulation in organs and the possibility to accumulate in the tumor. These results warrant further studies of radioiodinated carboxylic and hydroxamic MNIP inhibitor tracers as potential SPECT tumor imaging agents. Copyright 2004 Elsevier Inc. All rights reserved.

CC Enzymes - General and comparative studies: coenzymes 10802  
 Pathology - Therapy 12512  
 Pharmacology - General 22002  
 Neoplasms - Pathology, clinical aspects and systemic effects 24004

IT Major Concepts  
 Enzymology (Biochemistry and Molecular Biophysics); Methods and Techniques; Pharmacology; Tumor Biology

IT Chemicals & Biochemicals  
 2-(4'-iodo-biphenyl-4-sulfonylamino)-3-(1H-indol-3-yl)-propionamide: biodistribution, carboxylic matrix metalloproteinase inhibitor tracer, hydroxamic matrix metalloproteinase inhibitor tracer, iodine-123-labeled, radioiodinated, synthesis, tumor imaging agents, pharmaceutical; 2-(4'-iodo-biphenyl-4-sulfonylamino)-3-(1H-indol-3-yl)-propionic acid: biodistribution, carboxylic matrix metalloproteinase inhibitor tracer, hydroxamic matrix metalloproteinase inhibitor tracer, iodine-123-labeled, radioiodinated, synthesis, tumor

**imaging agents, pharmaceutical**

**IT Methods & Equipment**  
single photon emission computed tomography [SPECT]: imaging and microscopy techniques, laboratory techniques; zymography: electrophoretic techniques, laboratory techniques

L51 ANSWER 42 OF 85 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

**ACCESSION NUMBER:** 2004:173933 BIOSIS  
**DOCUMENT NUMBER:** PREV200400175275  
**TITLE:** **Succinylhydroxamic** derivatives of alpha-amino acids as **MMP** inhibitors. Study of complex-formation equilibria with Cu<sup>2+</sup>, Ni<sup>2+</sup> and Zn<sup>2+</sup>.  
**AUTHOR(S):** Tegoni, Matteo; Dallavalle, Francesco; Santos, M. Amelia [Reprint Author]  
**CORPORATE SOURCE:** Centro de Quimica Estrutural, Instituto Superior Tecnico, Av Rovisco Pais 1, 1049-001, Lisboa, Portugal masantos@ist.utl.pt  
**SOURCE:** Journal of Inorganic Biochemistry, (February 2004) Vol. 98, No. 2, pp. 209-218. print.  
ISSN: 0162-0134 (ISSN print).  
**DOCUMENT TYPE:** Article  
**LANGUAGE:** English  
**ENTRY DATE:** Entered STN: 31 Mar 2004  
Last Updated on STN: 31 Mar 2004

**ED** Entered STN: 31 Mar 2004  
Last Updated on STN: 31 Mar 2004

**AB** A series of Pro- and Phe-succinyl **hydroxamate** derivatives, whose nanomolar inhibitory activity towards a series of **matrix metalloproteinases (MMPs)** was previously reported, have been studied and described herein in their interaction with Cu<sup>2+</sup>, Zn<sup>2+</sup>, Ni<sup>2+</sup> in aqueous solution, by using potentiometric, spectroscopic and ESI-MS (electrospray ionization mass) spectrometric techniques. A systematic study at various ligand-to-metal molar ratios allowed the determination of the stability constants of the complexes as well as the estimation of the coordination modes. The similarity in the biological activity of these compounds seems to be paralleled by the identical metal-complexation behaviour at neutral pH, namely in terms of chelating effectiveness and coordination modes, irrespective of the presence of one carboxylic or **hydroxamate** as extra groups, or also of the type of amino-acid residue at the other flank of the succinyl chain, which seems to be enough away from the succinyl **hydroxamate** metal-binding group. The stability order of the metal complexes with these ligands follows the Irving-Williams trend for this type of complex systems. Noteworthy is the identification of an interesting pentanuclear copper(II) species with the **monohydroxamic** ligands which structure was ascribed to a 12-metallacrown-4.

**CC** Biochemistry studies - Minerals 10069  
Enzymes - General and comparative studies: coenzymes 10802

**IT Major Concepts**  
Enzymology (Biochemistry and Molecular Biophysics)

**IT Chemicals & Biochemicals**  
copper ion; **matrix metalloproteinase: inhibition**; nickel ion; **phenylalanine-succinyl hydroxamate derivative: enzyme inhibitor**; proline-succinyl **hydroxamate derivative: enzyme inhibitor**; zinc ion

**IT Methods & Equipment**  
electrospray ionization mass spectrometry: laboratory techniques, spectrum analysis techniques; potentiometry: laboratory techniques; spectrophotometry: laboratory techniques, spectrum analysis techniques;

RN spectropolarimetry: laboratory techniques, spectrum analysis techniques  
 15158-11-9 (copper ion)  
 141907-41-7 (**matrix metalloproteinase**)  
 14701-22-5 (nickel ion)  
 23713-49-7 (zinc ion)

L51 ANSWER 43 OF 85 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on  
 STN  
 ACCESSION NUMBER: 2004:118406 BIOSIS  
 DOCUMENT NUMBER: PREV200400123646  
 TITLE: Reduction of experimental laser-induced choroidal neovascularization by orally administered BPHA, a selective **metalloproteinase inhibitor**.  
 AUTHOR(S): Kohri, Takashi [Reprint Author]; Moriwaki, Mitsuyasu; Nakajima, Masatoshi; Tabuchi, Hitoshi; Shiraki, Kunihiko  
 CORPORATE SOURCE: Department of Ophthalmology, Graduate School of Medicine, Osaka City University, 1-4-3 Asahimachi, Abeno-ku, 545-8585, Osaka City, Japan  
 kohri@med.osaka-cu.ac.jp  
 SOURCE: Graefe's Archive for Clinical and Experimental Ophthalmology, (November 2003) Vol. 241, No. 11, pp. 943-952. print.  
 DOCUMENT TYPE: Article  
 LANGUAGE: English  
 ENTRY DATE: Entered STN: 3 Mar 2004  
 Last Updated on STN: 3 Mar 2004  
 ED Entered STN: 3 Mar 2004  
 Last Updated on STN: 3 Mar 2004  
 AB Background: N-Biphenyl sulfonyl-phenylalanine hydroxamic acid (BPHA), a synthetic, selective **matrix metalloproteinase (MMP)-2, -9, -14 inhibitor**, has been reported to show significant antiangiogenic activity without unpleasant adverse effects. After film in situ zymography (FIZ) and conventional zymography were performed to detect **MMP** in experimental choroidal neovascularizations (CNVs), we studied the reducible effect of BPHA on CNVs. Methods: Using FIZ, the gelatinolytic activity of **MMP** and BPHA-reduction on gelatinolysis were examined in diode-laser-induced CNV lesions in a total of 22 male Brown Norway rats. The **MMP** subtypes were studied in the CNV lesions of three rats using conventional zymography. Vehicle solution only or 25-, 50-, or 100 mg/kg-body-weight of BPHA was administered orally twice daily for 14 days after the laser photocoagulation in 18 rats, respectively. Fluorescein angiograms were taken, and the late hyperfluorescence of CNVs was given scores by three researchers using four grades. The thickness of CNV lesions was studied histologically. Results: In laser-induced CNVs, the gelatinolytic activity of **MMP** and reduction of gelatinolysis by BPHA were observed on FIZ, and **MMP-2** and proMMP-2 were identified by conventional zymography. The scores given to the late dye leakage and staining on angiograms were lower in the BPHA-treated groups ( $p<0.01$ ) than in the controls, and the effect appeared to be dose-dependent. Similarly, the CNV lesions in the BPHA-treated groups were less thick than in the controls ( $p<0.01$ ). Conclusions: **MMP-2** played a role in laser-induced CNV development, and administration of BPHA reduced the experimental CNVs.  
 CC Enzymes - General and comparative studies: coenzymes 10802  
 Pathology - Therapy 12512  
 Sense organs - Physiology and biochemistry 20004  
 Sense organs - Pathology 20006  
 Pharmacology - General 22002

IT Major Concepts  
 Methods and Techniques; Pharmacology; Sense Organs (Sensory Reception)

IT Diseases  
 experimental laser-induced choroidal neovascularization: eye disease,  
 injury, complications

IT Chemicals & Biochemicals  
*N-biphenyl sulfonyl-phenylalanine*  
*hydroxamic acid [BPFA]: enzyme inhibitor-drug; matrix*  
*metalloproteinase-2 [MMP-2]*

IT Methods & Equipment  
 conventional zymography: laboratory techniques

IT Miscellaneous Descriptors  
 gelatinolysis

ORGN Classifier  
 Muridae 86375  
 Super Taxa  
 Rodentia; Mammalia; Vertebrata; Chordata; Animalia  
 Organism Name  
 Brown Norway rat (common): male  
 Taxa Notes  
 Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals,  
 Rodents, Vertebrates

RN 146480-35-5 (**matrix metalloproteinase-2**)  
 146480-35-5 (**MMP-2**)

L51 ANSWER 44 OF 85 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on  
 STN

ACCESSION NUMBER: 2003:127804 BIOSIS  
 DOCUMENT NUMBER: PREV200300127804  
 TITLE: Synthesis and structure-activity relationships of  
 5,6,7,8-tetrahydropyrido(3,4-b)pyrazine-based  
**hydroxamic acids** as HB-EGF shedding inhibitors.  
 AUTHOR(S): Yoshiizumi, Kazuya [Reprint Author]; Yamamoto, Minoru;  
 Miyasaka, Tomohiro; Ito, Yasuko; Kumihara, Hiroshi; Sawa,  
 Masaaki; Kiyoi, Takao; Yamamoto, Takeshi; Nakajima, Fumio;  
 Hirayama, Ryoichi; Kondo, Hirosato; Ishibushi, Etsuko;  
 Ohmoto, Hiroshi; Inoue, Yoshimasa; Yoshino, Kohichiro  
 CORPORATE SOURCE: Medicinal Chemistry Department, Organon Laboratories Ltd.,  
 Newhouse, Motherwell, Lanarkshire, ML1 5SH, UK  
 k.yoshiizumi@organon.nhe.akzonobel.nl  
 SOURCE: Bioorganic & Medicinal Chemistry, (6 February 2003) Vol.  
 11, No. 3, pp. 433-450. print.  
 ISSN: 0968-0896 (ISSN print).  
 DOCUMENT TYPE: Article  
 LANGUAGE: English  
 ENTRY DATE: Entered STN: 5 Mar 2003  
 Last Updated on STN: 5 Mar 2003  
 ED Entered STN: 5 Mar 2003  
 Last Updated on STN: 5 Mar 2003  
 AB HB-EGF Shedding inhibitors have been expected to become effective  
 medicines for skin diseases caused by the proliferation of keratinocytes.  
 In order to discover novel HB-EGF shedding inhibitors and clarify their  
 structure-activity relationships, 5,6,7,8-tetrahydronaphthyridine  
 -based **hydroxamic acid** and 5,6,7,8-tetrahydropyrido(3,4-  
 b)pyrazine-based **hydroxamic acids** have been synthesized. Among  
 the synthesized compounds, the ethoxyethoxy derivative and the  
 methoxypropoxy derivative exhibited much more potent HB-EGF shedding  
 inhibitory activity than CGS 27023A. The structural modification of  
 5,6,7,8-tetrahydropyrido(3,4-b)pyrazine-based **hydroxamic acids**  
 enabled us to establish the following structure-activity relationships;

the existences of the **hydroxamic acid**, the sulfonamide, and the **phenyl** moieties are crucial for a potent HB-EGF shedding inhibitory activity, and the stereochemistry of the alpha carbon of **hydroxamic acid** is also important. In addition, from the comparison of their HB-EGF shedding inhibitory activities with their **MMPs** inhibitory activities, we found that the S1' pocket of the responsible enzyme for HB-EGF shedding is deep unlike that of **MMP -1**.

CC Cytology - Animal 02506  
 Cytology - Human 02508  
 Biochemistry studies - Proteins, peptides and amino acids 10064  
 Pathology - Therapy 12512  
 Endocrine - General 17002  
 Integumentary system - Physiology and biochemistry 18504  
 Integumentary system - Pathology 18506  
 Pharmacology - General 22002  
 Pharmacology - Clinical pharmacology 22005  
 Pharmacology - Integumentary system, dental and oral biology 22020  
 IT Major Concepts  
     Integumentary System (Chemical Coordination and Homeostasis);  
     Pharmacology  
 IT Parts, Structures, & Systems of Organisms  
     epidermis: integumentary system; keratinocytes: integumentary system  
 IT Diseases  
     skin diseases: integumentary system disease  
     Skin Diseases (MeSH)  
 IT Chemicals & Biochemicals  
     5,6,7,8-tetrahydropyrido[3,4-b]pyrazine; 5,6,7,8-tetrahydropyrido[3,4-b]pyrazine-based **hydroxamic acids**: dermatological-drug, heparin-binding-epidermal growth factor shedding inhibitors, structure-activity relationships, synthesis; CGS 27023A: dermatological-drug; a disintegrin and **metalloproteinases**; amphiregulin; epidermal growth factor; fibroblast growth factor-1; heparin-binding-epidermal growth factor; hepatocyte growth factor; **hydroxamic acid**; **matrix metalloproteinase-1**; transforming growth factor alpha  
 ORGN Classifier  
     Hominidae 86215  
 Super Taxa  
     Primates; Mammalia; Vertebrata; Chordata; Animalia  
 Organism Name  
     human (common)  
 Taxa Notes  
     Animals, Chordates, Humans, Mammals, Primates, Vertebrates  
 RN 169799-04-6 (CGS 27023A)  
 117147-70-3 (amphiregulin)  
 62229-50-9 (epidermal growth factor)  
 106096-92-8 (fibroblast growth factor-1)  
 9001-12-1 (**matrix metalloproteinase-1**)

L51 ANSWER 45 OF 85 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on  
 STN  
 ACCESSION NUMBER: 2003:60921 BIOSIS  
 DOCUMENT NUMBER: PREV200300060921  
 TITLE: NMR-based modification of **matrix metalloproteinase** inhibitors with improved bioavailability.  
 AUTHOR(S): Hajduk, Philip J.; Shuker, Suzanne B.; Nettesheim, David G.; Craig, Richard; Augeri, David J.; Betebenner, David; Albert, Daniel H.; Guo, Yan; Meadows, Robert P.; Xu,

CORPORATE SOURCE: Lianhong; Michaelides, Michael; Davidsen, Steven K.; Fesik, Stephen W. [Reprint Author]  
 Abbott Laboratories, 100 Abbott Park Road, D460, AP-10,  
 Abbott Park, IL, 60064-3500, USA  
 stephen.fesik@abbott.com

SOURCE: Journal of Medicinal Chemistry, (December 19 2002) Vol. 45,  
 No. 26, pp. 5628-5639. print.  
 ISSN: 0022-2623 (ISSN print).

DOCUMENT TYPE: Article  
 LANGUAGE: English  
 ENTRY DATE: Entered STN: 22 Jan 2003  
 Last Updated on STN: 22 Jan 2003

ED    Entered STN: 22 Jan 2003  
 Last Updated on STN: 22 Jan 2003

AB    The NMR-based discovery of biaryl **hydroxamate** inhibitors of the matrix **metalloproteinase stromelysin (MMP-3)** has been previously described (Hajduk et al. J. Am. Chemical Society 1997, 119, 5818-5827). While potent in vitro, these inhibitors exhibited no in vivo activity due, at least in part, to the poor pharmacokinetic properties of the **alkylhydroxamate** moiety. To circumvent this liability, NMR-based screening was implemented to identify alternative zinc-chelating groups. Using this technique, **1-naphthyl hydroxamate** was found to bind tightly to the protein (KD=50 μM) and was identified as a candidate for incorporation into the lead series. On the basis of NMR-derived structural information, the **naphthyl hydroxamate** and biaryl fragments were linked together to yield inhibitors of this enzyme that exhibited improved bioavailability. These studies demonstrate that the NMR-based screening of fragments can be effectively applied to improve the physicochemical or pharmacokinetic profile of lead compounds.

CC    Biochemistry studies - General    10060  
 Biochemistry studies - Minerals    10069

IT    Major Concepts  
 Biochemistry and Molecular Biophysics

IT    Chemicals & Biochemicals  
 1-naphthyl hydroxamate; matrix  
 metalloproteinase inhibitors: bioavailability; matrix  
 metalloproteinase-3 [stromelysin]; zinc

IT    Methods & Equipment  
 NMR: laboratory techniques, spectrum analysis techniques

RN    79955-99-0 (matrix metalloproteinase-3)  
 79955-99-0 (stromelysin)  
 7440-66-6 (zinc)

L51 ANSWER 46 OF 85 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on  
 STN

ACCESSION NUMBER: 2002:392198 BIOSIS  
 DOCUMENT NUMBER: PREV200200392198

TITLE: Selective matrix metalloproteinase inhibitor, N-biphenyl sulfonyl phenylalanine hydroxamic acid, inhibits the migration of CD4+ T lymphocytes in patients with HTLV-I-associated myopathy.

AUTHOR(S): Ikegami, Mayumi; Umehara, Fujio [Reprint author]; Ikegami, Naohito; Maekawa, Ryuji; Osame, Mitsuhiro

CORPORATE SOURCE: The Third Department of Internal Medicine, Kagoshima University, School of Medicine, Sakuragaoka 8-35-1, 890, Kagoshima, Japan  
 umehara@m2.kufm.kagoshima-u.ac.jp

SOURCE: Journal of Neuroimmunology, (June, 2002) Vol. 127, No. 1-2,

pp. 134-138. print.  
 CODEN: JNRIDW. ISSN: 0165-5728.

DOCUMENT TYPE:

Article

LANGUAGE:

English

ENTRY DATE:

Entered STN: 17 Jul 2002

Last Updated on STN: 17 Jul 2002

ED Entered STN: 17 Jul 2002

Last Updated on STN: 17 Jul 2002

AB **Matrix metalloproteinases (MMPs)** have been reported to be involved in various inflammatory disorders. Previous studies revealed that **MMP-2** and **MMP-9** might play important roles in the breakdown of the blood-brain barrier (BBB) in the central nervous system (CNS) of patients with HTLV-I-associated myelopathy (HAM)/tropical spastic paraparesis (TSP). **N-Biphenyl sulfonyl-phenylalanine hydroxamic acid (BPNA)** selectively inhibits **MMP-2**, -9 and -14, but not **MMP-1**, -3 and -7. In the present study, we examined whether or not the selective **MMP** inhibitor BPNA could inhibit the heightened migrating activity of CD4+ T cells in HAM/TSP patients. The migration assay using an invasion chamber showed that migration of CD4+ T cells in HAM/TSP patients was inhibited by 25  $\mu$ M BPNA. In addition, the inhibitory ratio of migrating CD4+ lymphocytes was higher in HAM patients compared to normal controls. These results suggest that the selective **MMP** inhibitor BPNA has therapeutic potential for HAM/TSP.

CC Cytology - Animal 02506

Cytology - Human 02508

Enzymes - General and comparative studies: coenzymes 10802

Cardiovascular system - Physiology and biochemistry 14504

Blood - Blood and lymph studies 15002

Blood - Blood cell studies 15004

Muscle - Pathology 17506

Bones, joints, fasciae, connective and adipose tissue - Pathology 18006

Nervous system - Physiology and biochemistry 20504

Nervous system - Pathology 20506

Virology - Animal host viruses 33506

Immunology - General and methods 34502

Immunology - Immunopathology, tissue immunology 34508

Medical and clinical microbiology - Virology 36006

IT Major Concepts

Clinical Immunology (Human Medicine, Medical Sciences); Infection;  
 Neurology (Human Medicine, Medical Sciences); Orthopedics (Human  
 Medicine, Medical Sciences)

IT Parts, Structures, &amp; Systems of Organisms

CD4-positive T lymphocytes: blood and lymphatics, immune system,  
 inhibition, migration; blood-brain barrier: circulatory system, nervous  
 system; central nervous system: nervous system

IT Diseases

human T-cell lymphotropic virus type I-associated myelopathy: muscle  
 disease, nervous system disease, viral disease, tropical spastic  
 paraparesis

Paraparesis, Tropical Spastic (MeSH)

IT Chemicals &amp; Biochemicals

**N-biphenyl sulfonyl phenylalanine**  
**hydroxamic acid**: selective matrix  
**metalloproteinase inhibitor**; **matrix metalloproteinase-2**  
 $;$  **matrix metalloproteinase-9**

ORGN Classifier

Hominidae 86215

Super Taxa

Primates; Mammalia; Vertebrata; Chordata; Animalia

Organism Name  
 human: patient  
 Taxa Notes  
 Animals, Chordates, Humans, Mammals, Primates, Vertebrates  
 ORGN Classifier  
 Retroviridae 03305  
 Super Taxa  
 DNA and RNA Reverse Transcribing Viruses; Viruses; Microorganisms  
 Organism Name  
 human T-cell lymphotropic virus type I: pathogen  
 Taxa Notes  
 DNA and RNA Reverse Transcribing Viruses, Microorganisms, Viruses  
 RN 146480-35-5 (matrix metalloproteinase-2)  
 146480-36-6 (matrix metalloproteinase-9)

L51 ANSWER 47 OF 85 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on  
 STN

ACCESSION NUMBER: 2001:522206 BIOSIS  
 DOCUMENT NUMBER: PREV200100522206  
 TITLE: Discovery of macrocyclic hydroxamic acids containing biphenylmethyl derivatives at P1', a series of selective TNF-alpha converting enzyme inhibitors with potent cellular activity in the inhibition of TNF-alpha release.  
 AUTHOR(S): Xue, Chu-Biao [Reprint author]; He, Xiaohua; Corbett, Ronald L.; Roderick, John; Wasserman, Zelda R.; Liu, Rui-Qin; Jaffee, Bruce D.; Covington, Maryanne B.; Qian, Mingxin; Trzaskos, James M.; Newton, Robert C.; Magolda, Ronald L.; Wexler, Ruth R.; Decicco, Carl P.  
 CORPORATE SOURCE: Experimental Station, DuPont Pharmaceuticals Company, Wilmington, DE, 19880-0500, USA  
 chu-biao.xue@dupontpharma.com  
 SOURCE: Journal of Medicinal Chemistry, (October 11, 2001) Vol. 44, No. 21, pp. 3351-3354. print.  
 CODEN: JMCMAR. ISSN: 0022-2623.  
 DOCUMENT TYPE: Article  
 LANGUAGE: English  
 ENTRY DATE: Entered STN: 7 Nov 2001  
 Last Updated on STN: 23 Feb 2002  
 ED Entered STN: 7 Nov 2001  
 Last Updated on STN: 23 Feb 2002  
 AB SAR exploration at P1' using an anti-succinate-based macrocyclic hydroxamic acid as a template led to the identification of several bulky biphenylmethyl P1' derivatives which confer potent porcine TACE and anti-TNF-alpha cellular activities with high selectivity versus most of the MMPs screened. Our studies demonstrate for the first time that TACE has a larger S1' pocket in comparison to MMPs and that potent and selective TACE inhibitors can be achieved by incorporation of sterically bulky P1' residues.  
 CC Biochemistry studies - Proteins, peptides and amino acids 10064  
 Pathology - Therapy 12512  
 Pharmacology - General 22002  
 IT Major Concepts  
 Pharmacology  
 IT Chemicals & Biochemicals  
 MMP; TNF-alpha converting enzyme inhibitors; biphenylmethyl derivatives; macrocyclic hydroxamic acids: discovery, potent cellular activity;

## tumor necrosis factor-alpha: release

IT Methods & Equipment  
chemical synthesis: synthetic method

L51 ANSWER 48 OF 85 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 2000:261915 BIOSIS  
DOCUMENT NUMBER: PREV200000261915  
TITLE: Protease inhibitors: Synthesis of potent bacterial collagenase and **matrix metalloproteinase** inhibitors incorporating N-4-nitrobenzylsulfonylglycine hydroxamate moieties.  
AUTHOR(S): Scozzafava, Andrea; Supuran, Claudiu T. [Reprint author]  
CORPORATE SOURCE: Laboratorio di Chimica Inorganica e Bioinorganica, Universita degli Studi, Via Gino Capponi 7, I-50121, Florence, Italy  
SOURCE: Journal of Medicinal Chemistry, (May 4, 2000) Vol. 43, No. 9, pp. 1858-1865. print.  
CODEN: JMCMAR. ISSN: 0022-2623.  
DOCUMENT TYPE: Article  
LANGUAGE: English  
ENTRY DATE: Entered STN: 21 Jun 2000  
Last Updated on STN: 5 Jan 2002

ED Entered STN: 21 Jun 2000  
Last Updated on STN: 5 Jan 2002

AB A series of compounds was prepared by reaction of alkyl/arylsulfonyl halides with N-4-nitrobenzylglycine, followed by conversion of the COOH to the CONHOH group, with hydroxylamine in the presence of carbodiimides. Other structurally related compounds were obtained by reaction of N-4-nitrobenzylglycine with aryl isocyanates, arylsulfonyl isocyanates, or benzoyl isothiocyanate, followed by the similar conversion of the COOH into the CONHOH moiety. Another subseries of derivatives was prepared from sulfanilyl- or metanilyl-4-nitrobenzylglycine by reaction with arylsulfonyl isocyanates, followed by conversion of the COOH to the **hydroxamate** moiety. The new compounds were assayed as inhibitors of four **matrix metalloproteinases (MMPs)**, **MMP-1**, **MMP-2**, **MMP-8**, and **MMP-9**, and of the *Clostridium histolyticum* collagenase (ChC). Some of the prepared **hydroxamate** derivatives proved to be very effective collagenase/gelatinase inhibitors, depending on the substitution pattern at the sulfonamido moiety. Substitutions leading to best inhibitors of **MMP-1**, a short pocket enzyme, were those involving pentafluorophenylsulfonyl or 3-trifluoromethylphenylsulfonyl moieties at P1' (K<sub>I</sub>'s of 3-5 nM). For **MMP-2**, **MMP-8**, and **MMP-9** (deep-pocket enzymes), best inhibitors were especially those containing long perfluoroalkylsulfonyl and substituted-arylsulfonyl moieties, such as pentafluorophenylsulfonyl, 3- and 4-protected-aminophenylsulfonyl, 3- and 4-carboxyphenylsulfonyl, arylsulfonylureido, or arylsulfonylureidosulfanilyl/metanilyl moieties, at P1'. Bulkier groups in this position, such as 1- and 2-naphthyl, substituted-naphthyl, or quinolin-8-yl moieties among others, led to less effective **MMP**/ChC inhibitors. Best ChC inhibitors were again those containing pentafluorophenylsulfonyl or 3- and 4-protected-aminophenylsulfonyl P1' anchoring groups, suggesting that this protease is also a short-pocket wider-neck one (more similar to **MMP-1**). This study also proves that the 4-nitrobenzyl moiety is an efficient P2' anchoring moiety and that sulfonylureido, ureido, or carboxythioureido substitutions at P1' are also tolerated for obtaining potent sulfonylated amino acid **hydroxamate**-like **MMP**/ChC inhibitors.

CC Pharmacology - General 22002  
 Biochemistry methods - General 10050  
 Biochemistry studies - General 10060  
 Physiology and biochemistry of bacteria 31000  
 Biophysics - Molecular properties and macromolecules 10506  
 Enzymes - Physiological studies 10808  
 IT Major Concepts  
     Methods and Techniques; Pharmacology  
 IT Chemicals & Biochemicals  
     collagenase [EC 3.4.24.3]; matrix metalloproteinase-1;  
     matrix metalloproteinase-2; matrix metalloproteinase-8  
     ; matrix metalloproteinase-9; protease inhibitor: synthesis  
 IT Methods & Equipment  
     chemical synthesis: synthetic method  
 IT Miscellaneous Descriptors  
     drug development  
 ORGN Classifier  
     Endospore-forming Gram-Positives 07810  
 Super Taxa  
     Eubacteria; Bacteria; Microorganisms  
 Organism Name  
     Clostridium histolyticum  
 Taxa Notes  
     Bacteria, Eubacteria, Microorganisms  
 RN 9001-12-1 (collagenase)  
 9001-12-1 (EC 3.4.24.3)  
 9001-12-1 (matrix metalloproteinase-1)  
 146480-35-5 (matrix metalloproteinase-2)  
 9001-12-1 (matrix metalloproteinase-8)  
 146480-36-6 (matrix metalloproteinase-9)  
 37205-61-1 (protease inhibitor)

L51 ANSWER 49 OF 85 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on  
 STN  
 ACCESSION NUMBER: 2000:373549 BIOSIS  
 DOCUMENT NUMBER: PREV200000373549  
 TITLE: Protease inhibitors: Part 12. Synthesis of potent  
 matrix metalloproteinase and bacterial  
 collagenase inhibitors incorporating sulfonylated N-4-  
 nitrobenzyl-beta-alanine hydroxamate  
 moieties.  
 AUTHOR(S): Scozzafava, Andrea; Ilies, Marc A.; Manole, Gheorghe;  
 Supuran, Claudiu T. [Reprint author]  
 CORPORATE SOURCE: Laboratorio di Chimica Inorganica e Bioinorganica,  
 Universita degli Studi, Via Gino Capponi 7, I-50121,  
 Florence, Italy  
 SOURCE: European Journal of Pharmaceutical Sciences, (July, 2000)  
 Vol. 11, No. 1, pp. 69-79. print.  
 ISSN: 0928-0987.  
 DOCUMENT TYPE: Article  
 LANGUAGE: English  
 ENTRY DATE: Entered STN: 30 Aug 2000  
               Last Updated on STN: 8 Jan 2002  
 ED   Entered STN: 30 Aug 2000  
       Last Updated on STN: 8 Jan 2002  
 AB   N-4-Nitrobenzyl-beta-alanine was reacted with alkyl/arylsulfonyl halides,  
       followed by conversion of the COOH to the CONHOH group. Structurally  
       related compounds were obtained by reaction of N-4-nitrobenzyl-beta-  
       alanine with aryl isocyanates, arylsulfonyl isocyanates or benzoyl  
       isothiocyanate, followed by similar conversion of the COOH into the CONHOH

moiety. Another subseries of derivatives was prepared from sulfanilyl- or metanilyl-4-nitrobenzyl-beta-alanine by reaction with arylsulfonyl isocyanates, followed by the introduction of the **hydroxamate** moiety. The new compounds were assayed as inhibitors of four **matrix metalloproteinases (MMPs)**, **MMP-1**, **MMP-2**, **MMP-8** and **MMP-9**, and of the **Clostridium histolyticum collagenase (ChC)**. Some of the prepared **hydroxamate** derivatives proved to be very effective collagenase/gelatinase inhibitors, depending on the substitution pattern at the sulfonamido moiety. Substitutions leading to the best inhibitors of **MMP-1**, a short-pocket enzyme, were those involving pentafluorophenylsulfonyl or 3-trifluoromethyl-phenylsulfonyl at P1' (KI of 3-5 nM). For **MMP-2**, **MMP-8** and **MMP-9** (deep-pocket enzymes), the best inhibitors were those containing perfluoroalkylsulfonyl- and substituted-arylsulfonyl moieties, such as pentafluorophenylsulfonyl, 3- and 4-protected-aminophenylsulfonyl-, 3- and 4-carboxy-phenylsulfonyl-, arylsulfonylureido- or arylsulfonylureido-sulfanilyl-/metanilyl moieties at P1'. Bulkier groups in this position, such as 1- and 2-naphthyl-, substituted-naphthyl or quinoline-8-yl-moieties, among others, led to less effective **MMP/ChC** inhibitors. The best ChC inhibitors were again those containing pentafluorophenylsulfonyl, 3- and 4-protected-aminophenylsulfonyl P1' groups. This study demonstrates that the 4-nitrobenzyl moiety, investigated here for the first time, is an efficient P2' anchoring moiety, whereas the beta-alanyl scaffold can successfully replace the alpha-amino acyl one, for obtaining potent **MMP/ChC** inhibitors.

CC Physiology and biochemistry of bacteria 31000  
 Enzymes - General and comparative studies: coenzymes 10802  
 Pathology - Therapy 12512  
 Pharmacology - General 22002  
 IT Major Concepts  
 Pharmacology  
 IT Chemicals & Biochemicals  
 N-4-nitrobenzyl-beta-alanine; bacterial collagenase; bacterial collagenase inhibitors; **hydroxamate**; **matrix metalloproteinase-1 [MMP-1]**; **matrix metalloproteinase-2 [MMP-2]**; **matrix metalloproteinase-8 [MMP-8]**; **matrix metalloproteinase-9 [MMP-9]**; sulfonyl halide

ORGN Classifier  
 Endospore-forming Gram-Positives 07810  
 Super Taxa

Eubacteria; Bacteria; Microorganisms

Organism Name

*Clostridium histolyticum*

Taxa Notes

Bacteria, Eubacteria, Microorganisms

RN 9001-12-1 (**matrix metalloproteinase-1**)  
 9001-12-1 (**MMP-1**)  
 146480-35-5 (**matrix metalloproteinase-2**)  
 146480-35-5 (**MMP-2**)  
 9001-12-1 (**matrix metalloproteinase-8**)  
 9001-12-1 (**MMP-8**)  
 146480-36-6 (**matrix metalloproteinase-9**)  
 146480-36-6 (**MMP-9**)

L51 ANSWER 50 OF 85 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 2000:222734 BIOSIS

DOCUMENT NUMBER: PREV200000222734

TITLE: Novel 4-substituted phenylsulfanyl alkyl and aryl

**hydroxamic acid TACE and MMP  
inhibitors.**

AUTHOR(S): Davis, Jamie M. [Reprint author]; Venkatesan, Aranapakam [Reprint author]; Baker, Jannie L. [Reprint author]; Grosu, George T. [Reprint author]; Ellingboe, John W. [Reprint author]; Zask, Arie [Reprint author]; Skotnicki, Jerauld [Reprint author]; Killar, Loran; Cowling, Rebecca [Reprint author]; Jin, Guixian [Reprint author]; Sharr, Michelle; Sung, Amy

CORPORATE SOURCE: Chemical Sciences, Wyeth-Ayerst Research, 401 N. Middletown Rd, Pearl River, NY, 10965, USA

SOURCE: Abstracts of Papers American Chemical Society, (2000) Vol. 219, No. 1-2, pp. MED1 281. print.

Meeting Info.: 219th Meeting of the American Chemical Society. San Francisco, California, USA. March 26-30, 2000.

American Chemical Society.

CODEN: ACSRAL. ISSN: 0065-7727.

DOCUMENT TYPE: Conference; (Meeting)

Conference; Abstract; (Meeting Abstract)

LANGUAGE: English

ENTRY DATE: Entered STN: 31 May 2000

Last Updated on STN: 5 Jan 2002

ED    Entered STN: 31 May 2000

Last Updated on STN: 5 Jan 2002

CC    Pharmacology - General    22002

Biochemistry methods - General    10050

Biochemistry studies - General    10060

Biochemistry studies - Proteins, peptides and amino acids    10064

Enzymes - Physiological studies    10808

Pathology - Therapy    12512

Endocrine - General    17002

Immunology - Immunopathology, tissue immunology    34508

Bones, joints, fasciae, connective and adipose tissue - Pathology    18006

Metabolism - Minerals    13010

Pathology - General    12502

Enzymes - General and comparative studies: coenzymes    10802

General biology - Symposia, transactions and proceedings    00520

IT    Major Concepts

    Enzymology (Biochemistry and Molecular Biophysics); Immune System (Chemical Coordination and Homeostasis); Skeletal System (Movement and Support); Pharmacology

IT    Diseases

    rheumatoid arthritis: connective tissue disease, immune system disease, joint disease, treatment

    Arthritis, Rheumatoid (MeSH)

IT    Chemicals & Biochemicals

    4-substituted phenylsulfanyl alkyl hydroxamic acids: enzyme inhibitors, molecular properties, pharmaceuticals, pharmacological properties, synthesis; 4-substituted phenylsulfanyl aryl hydroxamic acids: enzyme inhibitors, molecular properties, pharmaceuticals, pharmacological properties, synthesis; cytokines; enzymes: inhibition

IT    Miscellaneous Descriptors

    inflammation; pathology; Meeting Abstract

ORGN Classifier

    Hominidae    86215

Super Taxa

    Primates; Mammalia; Vertebrata; Chordata; Animalia

Organism Name

    human

## Taxa Notes

Animals, Chordates, Humans, Mammals, Primates, Vertebrates

L51 ANSWER 51 OF 85 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 1998:396713 BIOSIS  
 DOCUMENT NUMBER: PREV199800396713

TITLE: Bis-substituted malonic acid **hydroxamate**  
 derivatives as inhibitors of human neutrophil collagenase (MMP8).

AUTHOR(S): Graf Von Roedern, Erich; Brandstetter, Hans; Engh, Richard A.; Bode, Wolfram; Grams, Frank; Moroder, Luis [Reprint author]

CORPORATE SOURCE: Max-Planck-Institut fuer Biochemie, Am Klopferspitz 18A, D-82152 Martinsried, Germany

SOURCE: Journal of Medicinal Chemistry, (July 30, 1998) Vol. 41, No. 16, pp. 3041-3047. print.  
 CODEN: JMCMAR. ISSN: 0022-2623.

DOCUMENT TYPE: Article  
 LANGUAGE: English  
 ENTRY DATE: Entered STN: 10 Sep 1998  
 Last Updated on STN: 21 Oct 1998

ED Entered STN: 10 Sep 1998  
 Last Updated on STN: 21 Oct 1998

AB Malonic acid hydroxamate derivatives bis-substituted at the methylene group were synthesized as potential nonpeptidic inhibitors of human neutrophil collagenase (MMP8). The presence of an aromatic residue both at the C2 malonic acid position and in the C-terminal tail for hydrophobic interactions with the surface-exposed S1 binding site and the S1' pocket of the enzyme, respectively, was found to be sufficient for submicromolar inhibition potencies. For optimal insertion of the aryl amide group into the hydrophobic S1' pocket, spacing of the C-terminal phenyl group by at least a 3C-chain was required. In view of these results the achiral indan-2,2-dicarboxylic acid was used to mimic the 2-benzyl-2-methylmalonic acid residue, and its derivatization to the **3-phenylpropyl** amide **hydroxamate** produced a potent, achiral, low-mass inhibitor of MMP8 ( $K_i = 0.3 \mu\text{M}$ ), the binding mode of which was unambiguously determined by X-ray crystallographic analysis.

CC Pharmacology - General 22002  
 Biochemistry methods - General 10050  
 Biochemistry studies - General 10060  
 Biophysics - General 10502  
 Enzymes - General and comparative studies: coenzymes 10802

IT Major Concepts  
 Enzymology (Biochemistry and Molecular Biophysics); Pharmacology

IT Chemicals & Biochemicals  
 malonic acid **hydroxamate**: bis-substituted, derivatives, synthesis, potency, enzyme inhibitor; **matrix metalloproteinase 8 [neutrophil collagenase]**: inhibition

IT Methods & Equipment  
 X-ray crystallography: determination method

IT Miscellaneous Descriptors  
 pharmaceuticals

ORGN Classifier  
 Hominidae 86215  
 Super Taxa  
 Primates; Mammalia; Vertebrata; Chordata; Animalia  
 Organism Name  
 human  
 Taxa Notes

Animals, Chordates, Humans, Mammals, Primates, Vertebrates  
 RN 9001-12-1 (**matrix metalloproteinase 8**)  
 9001-12-1 (neutrophil collagenase)

L51 ANSWER 52 OF 85 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on  
 STN

ACCESSION NUMBER: 1998:233045 BIOSIS  
 DOCUMENT NUMBER: PREV199800233045  
 TITLE: Inhibition of membrane-type 1 matrix  
**metalloproteinase by hydroxamate**  
 inhibitors: An examination of the subsite pocket.  
 AUTHOR(S): Yamamoto, Minoru; Tsujishita, Hideki; Hori, Noriyuki  
 [Reprint author]; Ohishi, Yuichi; Inoue, Shintaro; Ikeda,  
 Shoji [Reprint author]; Okada, Yasunori  
 CORPORATE SOURCE: New Drug Discovery Res. Lab., Kanebo Ltd., 1-5-90  
 Tomobuchi-Cho, Miyakojima-Ku, Osaka 534, Japan  
 SOURCE: Journal of Medicinal Chemistry, (April 9, 1998) Vol. 41,  
 No. 8, pp. 1209-1217. print.  
 CODEN: JMCMAR. ISSN: 0022-2623.

DOCUMENT TYPE: Article  
 LANGUAGE: English  
 ENTRY DATE: Entered STN: 20 May 1998  
 Last Updated on STN: 20 May 1998

ED Entered STN: 20 May 1998  
 Last Updated on STN: 20 May 1998

AB The membrane-type 1 matrix metalloproteinase (MT1-MMP) has been reported to mediate the activation of pro-gelatinase A (proMMP-2), which is associated with tumor proliferation and metastasis. MT1-MMP can also digest extracellular matrix (ECM) such as interstitial collagens, gelatin, and proteoglycan and thus may play an important role in pathophysiological digestion of ECM. We studied the inhibitory effect of various hydroxamate MMP inhibitors, including known inhibitors such as BB-94, BB-2516, GM6001, and Ro31-9790, on a deletion mutant of MT1-MMP lacking the transmembrane domain (DELTAMT1) to further characterize the enzyme and develop a selective inhibitor for MT1-MMP. The evaluation of the inhibitory activities of various hydroxamates reveals general structural profiles affecting selectivities toward MMPs. In particular, a longer side chain at the P1' position is preferable for the binding to MMP-2, -3, and -9 and MT1-MMP. For the P2' position, an alpha-branched alkyl group is critical for the binding toward DELTAMT1, while the introduction of a bulky group at the alpha-position of hydroxamic acid seems to diminish the activity against DELTAMT1. Summation of the data on the sensitivity of DELTAMT1 to various hydroxamate inhibitors indicates that (1) the volume of the S1' subsite of DELTAMT1 is similar to that of MMP-2, -3, and -9, which is bigger than that of MMP-1, and (2) the S1 and S2' subsites are narrower than those in other MMPs. On the basis of these results, the hydroxamates with a P1' phenylpropyl and P2' alpha-branched alkyl group were synthesized and evaluated for inhibitory activity. These inhibitors (1h,i) showed strong activity against DELTAMT1 over MMP-1, but no selectivity between DELTAMT1 and MMP-9. These results are explained using molecular modeling studies conducted on MT1-MMP.

CC Pharmacology - General 22002  
 Biochemistry methods - General 10050  
 Biochemistry studies - General 10060  
 Biophysics - General 10502  
 Enzymes - General and comparative studies: coenzymes 10802

IT Major Concepts

Enzymology (Biochemistry and Molecular Biophysics); Pharmacology  
 IT Chemicals & Biochemicals  
 membrane-type 1 matrix metalloproteinase [MT1-MMP]: deletion mutation, subsite pocket, transmembrane domain, inhibition; BB-2516: enzyme inhibitor-drug, hydroxymate MMP inhibitor, quantitative structure-activity relationships; BB-94: enzyme inhibitor-drug, hydroxymate MMP inhibitor, quantitative structure-activity relationships; GM6001: enzyme inhibitor-drug, hydroxymate MMP inhibitor, quantitative structure-activity relationships; Ro31-9790: enzyme inhibitor-drug, hydroxymate MMP inhibitor, quantitative structure-activity relationships  
 IT Miscellaneous Descriptors pharmaceutical industry; drug design  
 RN 161384-17-4 (membrane-type 1 matrix metalloproteinase)  
 161384-17-4 (MT1-MMP)  
 154039-60-8 (BB-2516)  
 130370-60-4 (BB-94)  
 145337-55-9 (Ro31-9790)  
 81669-70-7 (METALLOPROTEINASE)

L51 ANSWER 53 OF 85 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN  
 ACCESSION NUMBER: 2002:83343 BIOSIS  
 DOCUMENT NUMBER: PREV200200083343  
 TITLE: Biphenyl hydroxamate inhibitors of matrix metalloproteinases.  
 AUTHOR(S): Fesik, S. W. [Inventor]; Summers, J. B., Jr. [Inventor]; Davidsen, S. K. [Inventor]; Sheppard, G. S. [Inventor]; Steinman, D. H. [Inventor]; Carrera, G. M., Jr. [Inventor]; Florjancic, A. [Inventor]; Holms, J. H. [Inventor]  
 CORPORATE SOURCE: Gurnee, Ill., USA  
 ASSIGNEE: ABBOTT LABORATORIES  
 PATENT INFORMATION: US 5665777 19970909  
 SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (Sept. 9, 1997) Vol. 1202, No. 2, pp. 1389-1390. print.  
 CODEN: OGUPE7. ISSN: 0098-1133.  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 ENTRY DATE: Entered STN: 16 Jan 2002  
 Last Updated on STN: 25 Feb 2002  
 ED Entered STN: 16 Jan 2002  
 Last Updated on STN: 25 Feb 2002  
 NCL 514575000  
 CC Biochemistry studies - General 10060  
 Enzymes - General and comparative studies: coenzymes 10802  
 Pharmacology - General 22002  
 IT Major Concepts Biochemistry and Molecular Biophysics; Enzymology (Biochemistry and Molecular Biophysics); Pharmacology  
 IT Miscellaneous Descriptors ENZYME INHIBITOR AGENTS; MOLECULAR STRUCTURE; PHARMACEUTICALS

L51 ANSWER 54 OF 85 PASCAL COPYRIGHT 2005 INIST-CNRS. ALL RIGHTS RESERVED.  
 on STN  
 ACCESSION NUMBER: 2005-0390734 PASCAL  
 COPYRIGHT NOTICE: Copyright .COPYRGT. 2005 INIST-CNRS. All rights reserved.  
 TITLE (IN ENGLISH): Discovery of 3,3-dimethyl-5-hydroxypipeolic hydroxamate-based inhibitors of aggrecanase

AUTHOR: and **MMP-13**  
 NOE Mark C.; NATARAJAN Vijayalakshmi; SNOW Sheri L.;  
 MITCHELL Peter G.; LOPRESTI-MORROW Lori; REEVES Lisa  
 M.; YOCUM Sue A.; CARTY Thomas J.; BARBERIA John A.;  
 SWEENEY Francis J.; LIRAS Jennifer L.; VAUGHN Marcie;  
 HARDINK Joel R.; HAWKINS Joel M.; TOKAR Christopher  
 Pfizer Global Research and Development Groton  
 Laboratories, Eastern Point Road, Groton, CT 06340,  
 United States

CORPORATE SOURCE:

SOURCE: Bioorganic & medicinal chemistry letters : (Print),  
 (2005), 15(11), 2808-2811  
 ISSN: 0960-894X

DOCUMENT TYPE: Journal

BIBLIOGRAPHIC LEVEL: Analytic

COUNTRY: United Kingdom

LANGUAGE: English

NOTE: 1/2 p. ref. et notes

AVAILABILITY: INIST-22446, 354000124636920230

UP 20051010

AB A series of peptidic **hydroxamate** inhibitors of **MMP**-13 and aggrecanase was discovered based on screening known inhibitors of **TNF-α** converting enzyme (**TACE**). Potency versus aggrecanase was optimized by modification of the benzyloxyaryl-sulfonamide group. Incorporation of geminal alkyl substitution at the 3-position of the piperidine ring improved metabolic stability, presumably by increasing steric hindrance around the metabolically labile **hydroxamic** acid. This modification also resulted in dramatic improvement of aggrecanase activity with a slight reduction in selectivity versus **MMP-1**. Synthesis, structure activity relationships, and strategies to reduce metabolic clearance are described.

L51 ANSWER 55 OF 85 PASCAL COPYRIGHT 2005 INIST-CNRS. ALL RIGHTS RESERVED.  
 on STN

ACCESSION NUMBER: 2005-0251575 PASCAL

COPYRIGHT NOTICE: Copyright .COPYRGT. 2005 INIST-CNRS. All rights reserved.

TITLE (IN ENGLISH): Synthesis and SAR of diazepine and thiazepine **TACE** and **MMP** inhibitors

AUTHOR: ZASK Arie; KAPLAN Joshua; XUEMEI DU; MACEWAN Gloria; SANDANAYAKA Vincent; EUDY Nancy; LEVIN Jeremy; GUIXIAN JIN; JUN XU; CUMMONS Terri; BARONE Dauphine; AYRAL-KALOUSTIAN Semiramis; SKOTNICKI Jerauld Wyeth Research, 401 N. Middletown Road, Pearl River, NY 10965, United States; Wyeth Research, PO Box CN 8000, Princeton, NJ 08543, United States; Amgen, Seattle, WA 98101, United States

CORPORATE SOURCE:

SOURCE: Bioorganic- & medicinal chemistry letters : (Print), (2005), 15(6), 1641-1645  
 ISSN: 0960-894X

DOCUMENT TYPE: Journal

BIBLIOGRAPHIC LEVEL: Analytic

COUNTRY: United Kingdom

LANGUAGE: English

NOTE: 1/2 p. ref. et notes

AVAILABILITY: INIST-22446, 354000126328090210

UP 20050627

AB Potent and selective TACE and MMP inhibitors utilizing the diazepine and thiazepine ring systems were synthesized and evaluated for biological activity in *in vitro* and *in vivo* models of TNF- $\alpha$  release. Oral

activity in the mouse LPS model of TNF- $\alpha$  release was seen. Efficacy in the mouse collagen induced arthritis model was achieved with diazepine 20.

L51 ANSWER 56 OF 85 PASCAL COPYRIGHT 2005 INIST-CNRS. ALL RIGHTS RESERVED.  
on STN

ACCESSION NUMBER: 2004-0606858 PASCAL  
COPYRIGHT NOTICE: Copyright .COPYRGT. 2004 INIST-CNRS. All rights reserved.

TITLE (IN ENGLISH): Pyran-containing sulfonamide hydroxamic acids: Potent MMP inhibitors that spare MMP-1

AUTHOR: REITER Lawrence A.; ROBINSON Ralph P.; MCCLURE Kim F.; JONES Christopher S.; REESE Matthew R.; MITCHELL Peter G.; OTTERNESS Ivan G.; BLIVEN Marcia L.; LIRAS Jennifer; CORTINA Santo R.; DONAHUE Kathleen M.; ESKRA James D.; GRIFFITHS Richard J.; LAME Mary E.; LOPEZ-ANAYA Arturo; MARTINELLI Gary J.; MCGAHEE Shunda M.; YOCUM Sue A.; LOPRESTI-MORROW Lori L.; TOBIASSEN Lisa M.; VAUGHN-BOWSER Marcie L.

CORPORATE SOURCE: Pfizer Global Research & Development, Groton Laboratories, Eastern Point Road, Groton, CT 06340, United States; Pfizer Global Research & Development, Groton Laboratories, Eastern Point Road, Groton, CT 06340, United States

SOURCE: Bioorganic & medicinal chemistry letters : (Print), (2004), 14(13), 3389-3395  
ISSN: 0960-894X

DOCUMENT TYPE: Journal  
BIBLIOGRAPHIC LEVEL: Analytic  
COUNTRY: United Kingdom  
LANGUAGE: English  
NOTE: 3/4 ref. et notes  
AVAILABILITY: INIST-22446, 354000110389820030  
UP 20041223

AB The SAR of a series of sterically hindered sulfonamide hydroxamic acids with relatively large P.sub.1' groups is described. The compounds typically spare MMP-1 while being potent inhibitors of MMP-13. The metabolically more stable compounds in the series contain either a monocyclic or bicyclic pyran ring adjacent to the hydroxamate group. Despite the sparing of MMP-1, preclinical and clinical studies revealed that fibrosis in rats and MSS in humans is still produced.

L51 ANSWER 57 OF 85 PASCAL COPYRIGHT 2005 INIST-CNRS. ALL RIGHTS RESERVED.  
on STN

ACCESSION NUMBER: 2004-0593701 PASCAL  
COPYRIGHT NOTICE: Copyright .COPYRGT. 2004 INIST-CNRS. All rights reserved.

TITLE (IN ENGLISH): Sultam hydroxamates as novel matrix metalloproteinase inhibitors

AUTHOR: CHERNEY Robert J.; MO Ruowei; MEYER Dayton T.; HARDMAN Karl D.; LIU Rui-Qin; COVINGTON Maryanne B.; MINGXIN QIAN; WASSERMAN Zelda R.; CHRIST David D.; TRZASKOS James M.; NEWTON Robert C.; DECICCO Carl P.

CORPORATE SOURCE: Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, New Jersey 08543-4000, United States

SOURCE: Journal of medicinal chemistry : (Print), (2004), 47(12), 2981-2983, 17 refs.

DOCUMENT TYPE: ISSN: 0022-2623 CODEN: JMCMAR  
 BIBLIOGRAPHIC LEVEL: Journal; (letter to editor)  
 COUNTRY: Analytic  
 LANGUAGE: United States  
 AVAILABILITY: English  
 INIST-9165, 354000111973820060  
 UP 20041213  
 AB In this communication we describe the design, synthesis, and evaluation of novel sultam **hydroxamates** 4 as **MMP-2**, -9, and -13 inhibitors. Compound 26 was found to be an active inhibitor (**MMP-2 IC<sub>50</sub>** = 1 nM) with 1000-fold selectivity over **MMP-1** and good oral bioavailability (*F* = 43%) in mouse. An X-ray crystal structure of 26 in **MMP-13** confirms the key hydrogen bonds and prime side binding in the active site.

L51 ANSWER 58 OF 85 PASCAL COPYRIGHT 2005 INIST-CNRS. ALL RIGHTS RESERVED.  
 on STN

ACCESSION NUMBER: 2004-0551388 PASCAL  
 COPYRIGHT NOTICE: Copyright .COPYRGT. 2004 INIST-CNRS. All rights reserved.  
 TITLE (IN ENGLISH): Synthesis and biological activity of selective azasugar-based **TACE** inhibitors  
 AUTHOR: TSUKIDA Takahiro; MORIYAMA Hideki; INOUE Yoshimasa; KONDO Hirosato; YOSHINO Kohichiro; NISHIMURA Shin-Ichiro  
 CORPORATE SOURCE: Japan Bioindustry Association, Hokkaido Collaboration Center, N-21, W-12, Kita-Ku, Sapporo 001-0021, Japan; R&D Laboratories, Nippon Organon K.K., 1-5-90, Tomobuchi-cho, Miyakojima-ku, Osaka 534-0016, Japan; Division of Biological Sciences, Graduate School of Science, Hokkaido University, N-21, W-11, Kita-Ku, Sapporo 001-0021, Japan  
 SOURCE: Bioorganic & medicinal chemistry letters : (Print), (2004), 14(6), 1569-1572  
 ISSN: 0960-894X  
 DOCUMENT TYPE: Journal  
 BIBLIOGRAPHIC LEVEL: Analytic  
 COUNTRY: United Kingdom  
 LANGUAGE: English  
 NOTE: 1/2 p. ref. et notes  
 AVAILABILITY: INIST-22446, 354000116705780410  
 UP 20041117  
 AB A series of azasugar-based **hydroxamic** acid derivatives bearing 2R,3R,4R,5R-configuration is described. Compound 4c with 4,5-O-acetonide group showed excellent *in vitro* potency against **TACE**, with high selectivity over **MMP-1** and moderate selectivity over **MMP-3** and **MMP-9**.

L51 ANSWER 59 OF 85 PASCAL COPYRIGHT 2005 INIST-CNRS. ALL RIGHTS RESERVED.  
 on STN

ACCESSION NUMBER: 2004-0280279 PASCAL  
 COPYRIGHT NOTICE: Copyright .COPYRGT. 2004 INIST-CNRS. All rights reserved.  
 TITLE (IN ENGLISH): Cyclic phosphinamides and phosphonamides, novel series of potent **matrix metalloproteinase** inhibitors with antitumour activity  
 AUTHOR: DAHL SORENSEN Morten; BLAEHR Lars K. A.; CHRISTENSEN Mette K.; HOYER Thomas; LATINI Scilla; HJARNAA Pernille-Julia V.; BJOERKLING Fredrik  
 CORPORATE SOURCE: Medicinal Chemistry Research, LEO Pharma,

## SOURCE:

Industriparken 55, 2750 Ballerup, Denmark; Department of Biochemistry, LEO Pharma, Industriparken 55, 2750 Ballerup, Denmark; Department of Pharmacology, LED Pharma, Industriparken 55, 2750 Ballerup, Denmark  
Bioorganic & medicinal chemistry, (2003), 11(24), 5461-5484, 27 refs.

ISSN: 0968-0896

DOCUMENT TYPE: Journal

BIBLIOGRAPHIC LEVEL: Analytic

COUNTRY: United Kingdom

LANGUAGE: English

AVAILABILITY: INIST-26564, 354000114951660180

UP 20040629

AB The design, synthesis, and structure-activity relationship (SAR) of a series of novel nonpeptidic cyclic phosphon- and phosphinamide-based hydroxamic acids as inhibitors of matrix metalloproteinases MMP-1, MMP-3, and MMP-9 are presented. Based on modelling studies and X-ray analysis, a model of the binding mode of these novel compounds in the MMP active site was obtained. This model provided a rational explanation for the observed SAR data, which included a systematic study of different S1' directed substituents, zinc-complexing groups, chirality, and variation of the cyclic phosphon- and phosphinamide rings. The in vivo effect of four compounds in a human fibrosarcoma mouse model (HT1080) was evaluated and compared to that of a reference compound. Prinomastat. Inhibition of tumour growth was observed for all four compounds.

L51 ANSWER 60 OF 85 PASCAL COPYRIGHT 2005 INIST-CNRS. ALL RIGHTS RESERVED.  
on STN

ACCESSION NUMBER: 2004-0335214 PASCAL

COPYRIGHT NOTICE: Copyright .COPYRGT. 2004 INIST-CNRS. All rights reserved.

TITLE (IN ENGLISH): Rational design, synthesis and structure-activity relationships of a cyclic succinate series of TNF- $\alpha$  converting enzyme inhibitors. Part 1: Lead identification

AUTHOR: XUE Chu-Biao; XIAOHUA HE; RODERICK John; CORBETT Ronald L.; DUAN James J.-W.; LIU Rui-Qin; COVINGTON Maryanne B.; NEWTON Robert C.; TRZASKOS James M.; MAGOLDA Ronald L.; WEXLER Ruth R.; DECICCO Carl P.

CORPORATE SOURCE: Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ 08543-4000, United States

SOURCE: Bioorganic &amp; medicinal chemistry letters : (Print), (2003), 13(24), 4293-4297, 14 refs.

ISSN: 0960-894X

DOCUMENT TYPE: Journal

BIBLIOGRAPHIC LEVEL: Analytic

COUNTRY: United Kingdom

LANGUAGE: English

AVAILABILITY: INIST-22446, 354000114947060070

UP 20040719

AB Rational design based on the broad spectrum MMP inhibitor CGS 27023A led to the identification of a novel series of cyclic succinate TACE inhibitors. As a mixture of two enantiomers, the lead compound 17b exhibited potent enzyme activity ( $IC_{50} = 8 \text{ nM}$ ) in the inhibition of porcine TNF- $\alpha$  converting enzyme (pTACE) and excellent selectivity over aggrecanase and MMP-1, -2 and -9.

L51 ANSWER 61 OF 85 PASCAL COPYRIGHT 2005 INIST-CNRS. ALL RIGHTS RESERVED.

on STN  
 ACCESSION NUMBER: 2003-0434329 PASCAL  
 COPYRIGHT NOTICE: Copyright .COPYRGT. 2003 INIST-CNRS. All rights reserved.  
 TITLE (IN ENGLISH): Design, synthesis and evaluation of novel azasugar-based MMP/ADAM inhibitors  
 AUTHOR: MORIYAMA Hideki; TSUKIDA Takahiro; INOUE Yoshimasa; KONDO Hirosato; YOSHINO Kohichiro; NISHIMURA Shin-Ichiro  
 CORPORATE SOURCE: Japan Bioindustry Association, Hokkaido Collaboration Center, N-21, W-12, Kita-Ku, Sapporo 001-0021, Japan; R&D Laboratories, Nippon Organon K.K., 1-5-90, Tomobuchi-cho, Miyakojima-ku, Osaka 534-0016, Japan; Division of Biological Sciences, Graduate School of Science, Hokkaido University, N-21, W-12, Kita-Ku, Sapporo 001-0021, Japan  
 SOURCE: Bioorganic & medicinal chemistry letters : (Print), (2003), 13(16), 2741-2744  
 ISSN: 0960-894X  
 DOCUMENT TYPE: Journal  
 BIBLIOGRAPHIC LEVEL: Analytic  
 COUNTRY: United Kingdom  
 LANGUAGE: English  
 NOTE: 1/4 p. ref. et notes  
 AVAILABILITY: INIST-22446, 354000112228260260  
 UP 20031104  
 AB In order to verify whether azasugar would be a useful scaffold for inhibitory activity against metalloproteinases, we synthesized some azasugar-based compounds. As a result, it is clarified that azasugar moiety could function as successful inhibitor of matrix metalloproteinase-1, -3 and -9 and TACE.

L51 ANSWER 62 OF 85 PASCAL COPYRIGHT 2005 INIST-CNRS. ALL RIGHTS RESERVED.  
 on STN

ACCESSION NUMBER: 2003-0354461 PASCAL  
 COPYRIGHT NOTICE: Copyright .COPYRGT. 2003 INIST-CNRS. All rights reserved.  
 TITLE (IN ENGLISH): Synthesis and structure-activity relationship of N-substituted 4-arylsulfonylpiperidine-4-hydroxamic acids as novel, orally active matrix metalloproteinase inhibitors for the treatment of osteoarthritis  
 AUTHOR: ARANAPAKAM Venkatesan; DAVIS Jamie M.; GROSU George T.; BAKER Jannie; ELLINGBOE John; ZASK Arie; LEVIN Jeremy I.; SANDANAYAKA Vincent P.; DU Mila; SKOTNICKI Jerauld S.; DIJOSEPH John F.; SUNG Amy; SHARR Michele A.; KILLAR Loran M.; WALTER Thomas; GUIXIAN JIN; COWLING Rebecca; TILLETT Jeff; WEIGUANG ZHAO; MCDEVITT Joseph; ZHANG BAO XU  
 CORPORATE SOURCE: Wyeth Research, 401 N. Middletown Road, Pearl River, New York 10965, United States; Wyeth Research, P.O. Box CN-8000, Princeton, New Jersey 08543, United States  
 SOURCE: Journal of medicinal chemistry : (Print), / (2003), 46(12), 2376-2396, 17 refs.  
 ISSN: 0022-2623 CODEN: JMCMAR  
 DOCUMENT TYPE: Journal  
 BIBLIOGRAPHIC LEVEL: Analytic  
 COUNTRY: United States  
 LANGUAGE: English

AVAILABILITY: INIST-9165, 354000118233340140  
 UP 20030912  
 AB The matrix metalloproteinases (MMPs) are a family of zinc-containing endopeptidases that play a key role in both physiological and pathological tissue degradation. In our preceding paper, we have reported on a series of novel and orally active N-hydroxy- $\alpha$ -phenylsulfonyl-acetamide derivatives. However, these compounds had two drawbacks (moderate selectivity and chirality issues). To circumvent these two problems, a series of novel and orally active N-substituted 4-benzenesulfonylpiperidine-4-carboxylic acid hydroxyamide derivatives have been synthesized. The present paper deals with the synthesis and SAR of these compounds. Among the several compounds synthesized, derivative 55 turned out to be a potent, selective, and an orally active MMP inhibitor in the clinically relevant advanced rabbit osteoarthritis model. Detailed pharmacokinetics and metabolism data are described.

L51 ANSWER 63 OF 85 PASCAL COPYRIGHT 2005 INIST-CNRS. ALL RIGHTS RESERVED.  
 on STN  
 ACCESSION NUMBER: 2003-0260365 PASCAL  
 COPYRIGHT NOTICE: Copyright .COPYRGT. 2003 INIST-CNRS. All rights reserved.  
 TITLE (IN ENGLISH): Synthesis and SAR of bicyclic heteroaryl hydroxamic acid MMP and TACE inhibitors  
 AUTHOR: ZASK A.; GU Y.; ALBRIGHT J. D.; DU X.; HOGAN M.; LEVIN J. I.; CHEN J. M.; KILLAR L. M.; SUNG A.; DIJOSEPH J. F.; SHARR M. A.; ROTH C. E.; SKALA S.; JIN G.; COWLING R.; MOHLER K. M.; BARONE D.; BLACK R.; MARCH C.; SKOTNICKI J. S.  
 CORPORATE SOURCE: Wyeth-Ayerst Research, 401 N. Middletown Road, Pearl River, NY 10965, United States; Wyeth Research, PO Box CN800, Princeton, NJ 08543, United States; Immunex Corporation, Seattle, WA 98101, United States  
 SOURCE: Bioorganic & medicinal chemistry letters, (2003), 13(8), 1487-1490, 16 refs.  
 ISSN: 0960-894X  
 DOCUMENT TYPE: Journal  
 BIBLIOGRAPHIC LEVEL: Analytic  
 COUNTRY: United Kingdom  
 LANGUAGE: English  
 AVAILABILITY: INIST-22446, 354000110838630200  
 UP 20030626  
 AB Potent and selective bicyclic heteroaryl hydroxamic acid MMP and TACE inhibitors were synthesized by a novel convergent route. Selectivity and efficacy versus MMPs and TACE could be controlled by appropriate substitution on the scaffolds and by variation of the P1' group. Select compounds were found to be effective in in vivo models of arthritis.

L51 ANSWER 64 OF 85 PASCAL COPYRIGHT 2005 INIST-CNRS. ALL RIGHTS RESERVED.  
 on STN  
 ACCESSION NUMBER: 2004-0119346 PASCAL  
 COPYRIGHT NOTICE: Copyright .COPYRGT. 2004 INIST-CNRS. All rights reserved.  
 TITLE (IN ENGLISH): Screening of stress enhancer based on analysis of gene expression profiles: Enhancement of hyperthermia-induced tumor necrosis by an MMP-3 inhibitor  
 AUTHOR: KATO Naoki; KOBAYASHI Takeshi; HONDA Hiroyuki  
 CORPORATE SOURCE: Department of Biotechnology, School of Engineering,

SOURCE: Nagoya University, Furo-cho, Chikusa-ku, Nagoya  
 464-8603, Japan  
 Cancer science, (2003), 94(7), 644-649, 46 refs.  
 ISSN: 1347-9032

DOCUMENT TYPE: Journal  
 BIBLIOGRAPHIC LEVEL: Analytic  
 COUNTRY: Japan  
 LANGUAGE: English  
 AVAILABILITY: INIST-2432, 354000114967190140  
 UP 20040323

AB To improve the therapeutic benefit of hyperthermia, we examined changes of global gene expression after heat shock using DNA microarrays consisting of 12 814 clones. HeLa cells were treated for 1 h at 44°C and RNA was extracted from the cells 0, 3, 6, and 12 h after heat shock. The 664 genes that were up or down-regulated after heat shock were classified into 7 clusters using fuzzy adaptive resonance theory (fuzzy ART). There were 41 genes in two clusters that were induced in the early phase after heat shock. In addition to shock response genes, such as hsp70 and hsp40, the stress response genes c-jun, c-fos and egr-1 were expressed in the early phase after heat shock. We also found that expression of **matrix metalloproteinase 3 (MMP-3)** was enhanced during the early response. We therefore investigated the role of **MMP-3** in the heat shock response by examining HeLa cell survival after heat treatment in the presence and absence of an **MMP-3 inhibitor, N-isobutyl-N-(4-methoxyphenyl-sulfonyl)glycylhydroxamic acid (NNGH)** or **N-hydroxy-2(R)-[4-methoxysulfonyl](3-picollyl)amino]-3-methylbutaneamide hydrochloride (MMI270)**. The number of surviving cells 3 days after heat treatment significantly decreased, reaching 3.5% for NNGH and 0.2% for MMI270. These results indicate that the **MMP-3** inhibitors enhanced heat shock-induced cell death and behaved as stress enhancers in cancer cells. This valuable conclusion was reached as a direct result of the gene expression profiling that was performed in these studies.

L51 ANSWER 65 OF 85 PASCAL COPYRIGHT 2005 INIST-CNRS. ALL RIGHTS RESERVED.  
 on STN

ACCESSION NUMBER: 2002-0394701 PASCAL  
 COPYRIGHT NOTICE: Copyright .COPYRGT. 2002 INIST-CNRS. All rights reserved.  
 TITLE (IN ENGLISH): Synthesis and biological activity of selective pipecolic acid-based TNF- $\alpha$  converting enzyme (TACE) inhibitors  
 AUTHOR: LETAVIC Michael A.; AXT Matt Z.; BARBERIA John T.; CARTY Thomas J.; DANLEY Dennis E.; GEOGHEGAN Kieran F.; HALIM Nadia S.; HOTH Lise R.; KAMATH Ajith V.; LAIRD Ellen R.; LOPRESTI-MORROW Lori L.; MCCLURE Kim F.; MITCHELL Peter G.; NATARAJAN Vijayalakshmi; NOE Mark C.; PANDIT Jayvardhan; REEVES Lisa; SCHULTE Gayle K.; SNOW Sheri L.; SWEENEY Francis J.; TAN Douglas H.; YU Chul H.  
 CORPORATE SOURCE: Pfizer Global Research and Development, Groton Laboratories, Eastern Point Road, Groton, CT 06340, United States; Pfizer Global Research and Development, Groton Laboratories, Eastern Point Road, Groton, CT 06340, United States  
 SOURCE: Bioorganic & medicinal chemistry letters, (2002), 12(10), 1387-1390  
 ISSN: 0960-894X  
 DOCUMENT TYPE: Journal  
 BIBLIOGRAPHIC LEVEL: Analytic

COUNTRY: United Kingdom  
 LANGUAGE: English  
 NOTE: 3/4 p. ref. et notes  
 AVAILABILITY: INIST-22446, 354000101241630150  
 UP 20020821  
 AB A series of novel, selective TNF- $\alpha$  converting enzyme inhibitors based on 4-hydroxy and 5-hydroxy pipecolate hydroxamic acid scaffolds is described. The potency and selectivity of TACE inhibition is dramatically influenced by the nature of the sulfonamide group which interacts with the S1' site of the enzyme. Substituted 4-benzyloxybenzenesulfonamides exhibit excellent TACE potency with > 100 x selectivity over inhibition of matrix metalloprotease-1 (MMP-1). Alkyl substituents on the ortho position of the benzyl ether moiety give the most potent inhibition of TNF- $\alpha$  release in LPS-treated human whole blood.

L51 ANSWER 66 OF 85 PASCAL COPYRIGHT 2005 INIST-CNRS. ALL RIGHTS RESERVED.  
 on STN

ACCESSION NUMBER: 2002-0038400 PASCAL  
 COPYRIGHT NOTICE: Copyright .COPYRGT. 2002 INIST-CNRS. All rights reserved.

TITLE (IN ENGLISH):  $\alpha$ -Amino- $\beta$ -sulphone hydroxamates as potent MMP-13 inhibitors that spare MMP-1

AUTHOR: BECKER Daniel P.; BARTA Thomas E.; BEDELL Louis; DECRESCENZO Gary; FRESKOS John; GETMAN Daniel P.; HOCKERMAN Susan L.; LI Madeleine; MEHTA Pramod; MISCHKE Brent; MUNIE Grace E.; SWEARINGEN Craig; VILLAMIL Clara I.

CORPORATE SOURCE: Departments of Medicinal Chemistry and Inflammation-Oncology, Pharmacia Research & Development, 4901 Searle Parkway, Skokie, IL 60077, United States; Departments of Medicinal Chemistry and Inflammation-Oncology, Pharmacia Research & Development, 700 Chesterfield Village Parkway, St. Louis, MO 63198, United States

SOURCE: Bioorganic & medicinal chemistry letters, (2001), 11(20), 2719-2722  
 ISSN: 0960-894X

DOCUMENT TYPE: Journal

BIBLIOGRAPHIC LEVEL: Analytic

COUNTRY: United Kingdom

LANGUAGE: English

NOTE: 1/2 p. ref. et notes

AVAILABILITY: INIST-22446, 354000096443790130

UP 20020122

AB A series of  $\alpha$ -amino- $\beta$ -sulphone hydroxamates was prepared and evaluated for potency versus MMP-13 and selectivity versus MMP-1. Various substituents were employed on the  $\alpha$ -amino group (P.sub.1 position), as well as different groups attached to the sulphone group extending into P.sub.1'. Low nanomolar potency was obtained for MMP-13 with selectivity versus MMP-1 of > 1000 x for a number of analogues.

L51 ANSWER 67 OF 85 PASCAL COPYRIGHT 2005 INIST-CNRS. ALL RIGHTS RESERVED.  
 on STN

ACCESSION NUMBER: 2002-0100965 PASCAL  
 COPYRIGHT NOTICE: Copyright .COPYRGT. 2002 INIST-CNRS. All rights reserved.

TITLE (IN ENGLISH): QSAR of **matrix metalloproteinase inhibitor N-[(substituted phenyl)sulfonyl]-N-4-nitrobenzyl-glycine hydroxamates** using LFER model  
 AUTHOR: ROY Kunal; DIPAK KUMAR PAL; DE A. U.; SENGUPTA Chandana  
 CORPORATE SOURCE: Division of Pharmaceutical Chemistry, Seemanta Institute of Pharmaceutical Sciences, Jharpokharia, Mayurbhanj 757 086, Orissa, India; QSAR Lab, Division of Medicinal and Pharmaceutical Chemistry, Department of Pharmaceutical Technology, Jadavpur University, Calcutta 700 032, India  
 SOURCE: Drug design and discovery, (2001), 17(4), 315-323, 13 refs.  
 DOCUMENT TYPE: ISSN: 1055-9612  
 BIBLIOGRAPHIC LEVEL: Journal  
 COUNTRY: Analytic  
 Netherlands  
 LANGUAGE: English  
 AVAILABILITY: INIST-21182, 354000103159360020  
 UP 20020225  
 AB QSAR analyses of **matrix metalloproteinase (MMP)** inhibitor N-[(substituted phenyl)sulfonyl]-N-4-nitrobenzylglycine hydroxamates, recently reported by Scozzafava and Supuran, have been attempted using linear free energy related (LFER) model of Hansch to explore the contribution patterns of the phenyl ring substitutions (P.sub.1' anchoring site of the ligands) to the activities against MMP-1, -2, -8 and -9 (pC.sub.1, pC.sub.2, pC.sub.8 and pC.sub.9) and C. histolyticum collagenase (pC.sub.C.sub.h.sub.C) and also to find out relations among the activities. Multiple regression analyses applied on the data set reveal that electron withdrawing meta substituents and lipophilic ortho and meta substituents are conducive to pC.sub.1 while presence of substituents (larger than hydrogen) at vicinal positions on the phenyl ring and bulkier ortho substituents are detrimental to the activity. Again, the electronic and steric parameters of meta substituents ( $\sigma$ .sub.m and MR.sub.m) and lipophilicity parameter of ortho substituents ( $\pi$ .sub.o) contribute significantly to pC.sub.2, pC.sub.8 and pC.sub.9:  $\sigma$ .sub.m shows parabolic relationships (optimum  $\sigma$ .sub.m values being 0.518, 0.584 and 0.522 respectively) and steric bulk of meta substituents has negative impact while presence of hydrophilic groups at the ortho positions increases the activities. Further, presence of electron withdrawing meta substituents and hydrophilic para substituents is conducive to the C. histolyticum collagenase (pC.sub.C.sub.h.sub.C) activity. The study suggests that the structural and physicochemical requirements of the P.sub.1' anchoring site for the activities against MMP-2, -8 and -9 are highly intercorrelated and these are comparatively less correlated with those for the activities against MMP-1 and C. histolyticum collagenase.

L51 ANSWER 68 OF 85 PASCAL COPYRIGHT 2005 INIST-CNRS. ALL RIGHTS RESERVED.  
 on STN  
 ACCESSION NUMBER: 2001-0123337 PASCAL  
 COPYRIGHT NOTICE: Copyright .COPYRGT. 2001 INIST-CNRS. All rights reserved.  
 TITLE (IN ENGLISH): Heteroaryl and cycloalkyl sulfonamide hydroxamic acid inhibitors of **matrix metalloproteinases**  
 AUTHOR: LEVIN Jeremy I.; YANSONG GU; NELSON Frances C.; ZASK

Arie; DIJOSEPH John F.; SHARR Michele A.; SUNG Amy;  
 GUIXIAN JIN; COWLING Rebecca; CHANDA Pranab; COSMI  
 Scott; HSIAO Chu-Lai; EDRIS Wade; WILHELM James;  
 KILLAR Loran M.; SKOTNICKI Jerauld S.

CORPORATE SOURCE: Wyeth-Ayerst Research, 401 N. Middletown Road, Pearl River, NY 10965, United States; Wyeth-Ayerst Research, PO Box CN-8000, Princeton, NJ 08543, United States; Wyeth-Ayerst Research, Cambridge, MA 02140, United States

SOURCE: Bioorganic & medicinal chemistry letters, (2001), 11(2), 239-242  
 ISSN: 0960-894X

DOCUMENT TYPE: Journal

BIBLIOGRAPHIC LEVEL: Analytic

COUNTRY: United Kingdom

LANGUAGE: English

NOTE: 1/4 p. ref. et notes

AVAILABILITY: INIST-22446, 354000094861770360

UP 20010402

AB Heteroaryl and cycloalkyl sulfonamide-**hydroxamic acid**  
**MMP** inhibitors were investigated. Of these, the pyridyl analogue 2 is the most potent and selective inhibitor of **MMP-9** and **MMP-13** in vitro.

L51 ANSWER 69 OF 85 PASCAL COPYRIGHT 2005 INIST-CNRS. ALL RIGHTS RESERVED.  
 on STN

ACCESSION NUMBER: 2001-0122506 PASCAL

COPYRIGHT NOTICE: Copyright .COPYRGT. 2001 INIST-CNRS. All rights reserved.

TITLE (IN ENGLISH): The discovery of anthranilic acid-based **MMP** inhibitors. Part 1: SAR of the 3-position

AUTHOR: LEVIN Jeremy I.; DU Mila T.; DIJOSEPH John F.; KILLAR Loran M.; SUNG Amy; WALTER Thomas; SHARR Michele A.; ROTH Catherine E.; MOY Franklin J.; POWERS Robert; GUIXIAN JIN; COWLING Rebecca; SKOTNICKI Jerauld S.

CORPORATE SOURCE: Wyeth-Ayerst Research, 401 N. Middletown Road, Pearl River, NY 10965, United States; Wyeth-Ayerst Research, PO Box CN-8000, Princeton, NJ 08543, United States

SOURCE: Bioorganic & medicinal chemistry letters, (2001), 11(2), 235-238  
 ISSN: 0960-894X

DOCUMENT TYPE: Journal

BIBLIOGRAPHIC LEVEL: Analytic

COUNTRY: United Kingdom

LANGUAGE: English

NOTE: 1/2 p. ref. et notes

AVAILABILITY: INIST-22446, 354000094861770350

UP 20010402

AB A novel series of anthranilic acid-based inhibitors of **MMP-1**, **MMP-9**, and **MMP-13** was prepared and evaluated both in vitro and in vivo. The most potent compound, 6e, has in vivo activity in a rat sponge-wrapped cartilage model.

L51 ANSWER 70 OF 85 PASCAL COPYRIGHT 2005 INIST-CNRS. ALL RIGHTS RESERVED.  
 on STN

ACCESSION NUMBER: 2001-0328742 PASCAL

COPYRIGHT NOTICE: Copyright .COPYRGT. 2001 INIST-CNRS. All rights reserved.

TITLE (IN ENGLISH): Development of new **hydroxamate** **matrix metalloproteinase** inhibitors

AUTHOR: derived from functionalized 4-aminoprolines  
 NATCHUS Michael G.; BOOKLAND Roger G.; DE Biswanath;  
 ALMSTEAD Neil G.; PIKUL Stanislaw; JANUSZ Michael J.;  
 HEITMEYER Sandra A.; HOOKFIN Erin B.; HSIEH Lily C.;  
 DOWTY Martin E.; DIETSCH Charles R.; PATEL Vikram S.;  
 GARVER Susan M.; FEI GU; POKROSS Matthew E.; MIELING  
 Glen E.; BAKER Timothy R.; FOLTZ David J.; PENG Sean  
 X.; BORNES David M.; STROJNOWSKI Michael J.; TAIWO  
 Yetunde O.

SOURCE: Journal of medicinal chemistry : (Print), (2000),  
 43(26), 4948-4963, 32 refs.  
 ISSN: 0022-2623 CODEN: JMCMAR

DOCUMENT TYPE: Journal  
 BIBLIOGRAPHIC LEVEL: Analytic  
 COUNTRY: United States  
 LANGUAGE: English  
 AVAILABILITY: INIST-9165, 354000093588140050

UP 20010821

AB A series of **hydroxamates** was prepared from an aminoproline scaffold and tested for efficacy as **matrix metalloproteinase (MMP)** inhibitors. Detailed SAR for the series is reported for five enzymes within the **MMP** family, and a number of inhibitors, such as compound 47, display broad-spectrum activity with sub-nanomolar potency for some enzymes. Modifications of the P1' portion of the molecule played a key role in affecting both potency and selectivity within the **MMP** family. Longer-chain aliphatic substituents in this region of the molecule tended to increase potency for **MMP-3** and decrease potency for **MMP-1**, as exemplified by compounds 48-50, while aromatic substituents, as in compound 52, generated broad-spectrum inhibition. The data is rationalized based upon X-ray crystal data which is also presented. While the *in vitro* peroral absorption seemed to be less predictable, it tended to decrease with longer and more hydrophilic substituents. Finally, a rat model of osteoarthritis was used to evaluate the efficacy of these compounds, and a direct link was established between their pharmacokinetics and their *in vivo* efficacy.

L51 ANSWER 71 OF 85 PASCAL COPYRIGHT 2005 INIST-CNRS. ALL RIGHTS RESERVED.  
 on STN

ACCESSION NUMBER: 2000-0486235 PASCAL  
 COPYRIGHT NOTICE: Copyright .COPYRGT. 2000 INIST-CNRS. All rights reserved.

TITLE (IN ENGLISH): Inhibition of gelatinolytic activity in tumor tissues by synthetic **matrix metalloproteinase** inhibitor : Application of film *in situ* zymography

AUTHOR: IKEDA M.; MAEKAWA R.; TANAKA H.; MATSUMOTO M.; TAKEDA Y.; TAMURA Y.; NEMORI R.; YOSHIOKA T.

CORPORATE SOURCE: Shionogi Research Laboratories, Shionogi & Co., Ltd., Osaka 553-0002, Japan; Ashigara Research Laboratories, Fuji Photo Film Co., Ltd., Kanagawa 250-0193, Japan

SOURCE: Clinical cancer research, (2000), 6(8), 3290-3296, 25 refs.  
 ISSN: 1078-0432

DOCUMENT TYPE: Journal  
 BIBLIOGRAPHIC LEVEL: Analytic  
 COUNTRY: United States  
 LANGUAGE: English  
 AVAILABILITY: INIST-26073, 354000091246460440

UP 20001127

AB Inhibition of gelatinolytic activity in implanted tumor tissues by oral administration of N-biphenyl sulfonyl-phenylalanine hydroxamic acid (BPFA), a selective matrix metalloproteinase (MMP) inhibitor, was demonstrated by means of film in situ zymography (FIZ). Active-MMP-2 but not pro-MMP-2 showed gelatinolytic activity in FIZ, whereas both forms of MMP-2 were found to be active in conventional zymography. A mixture of either tissue inhibitors of metalloproteinase-2 or BPFA with active-MMP-2 resulted in inhibition of gelatinolytic activity in FIZ but not in zymography. Thus, FIZ, but not zymography, could detect net MMP activity in tumor tissues. When a specimen from Ma44 human lung cancer xenograft was subjected to FIZ, gelatinolytic activity was markedly detected with precise localization in the tumor tissues. The gelatinolytic activity detected in Ma44 tumor tissues was found to be mainly derived from MMPs because the gelatin-degrading activity was inhibited by pretreatment of the tumor specimen with MMP inhibitors. Oral administration of BPFA but not (-)BPFA, an enantiomer of BPFA lacking MMP inhibitory activity, successfully inhibited the MMP activity localized in Ma44 tumor tissues in both a dose-dependent and time-dependent manner. The data presented in this report showed for the first time that oral administration of synthetic MMP inhibitor could inhibit the net activity of MMP activity in tumor tissues, suggesting the usefulness of the FIZ technique for determining the effective dose of MMP inhibitor in clinical studies.

L51 ANSWER 72 OF 85 PASCAL COPYRIGHT 2005 INIST-CNRS. ALL RIGHTS RESERVED.  
on STN

ACCESSION NUMBER: 2000-0141069 PASCAL  
 COPYRIGHT NOTICE: Copyright .COPYRGT. 2000 INIST-CNRS. All rights reserved.  
 TITLE (IN ENGLISH): Design and synthesis of piperazine-based matrix metalloproteinase inhibitors  
 AUTHOR: MENYAN CHENG; BISWANATH DE; PIKUL S.; ALMSTEAD N. G.; NATCHUS M. G.; ANASTASIO M. V.; MCPHAIL S. J.; SNIDER C. E.; TAIWO Y. O.; LONGYIN CHEN; DUNAWAY C. M.; FEI GU; DOWTY M. E.; MIELING G. E.; JANUSZ M. J.; WANG-WEIGAND S.  
 CORPORATE SOURCE: Procter and Gamble Pharmaceuticals, Health Care Research Center, 8700 Mason-Montgomery Road, Mason, Ohio 45040, United States; Procter and Gamble, Corporate Research Division, Miami Valley Laboratories, Cincinnati, Ohio 45253, United States  
 SOURCE: Journal of medicinal chemistry : (Print), (2000), 43(3), 369-380, 16 refs.  
 ISSN: 0022-2623 CODEN: JMCMAR  
 DOCUMENT TYPE: Journal  
 BIBLIOGRAPHIC LEVEL: Analytic  
 COUNTRY: United States  
 LANGUAGE: English  
 AVAILABILITY: INIST-9165, 354000081959690060  
 UP 20001101  
 AB A new generation of cyclic matrix metalloproteinase (MMP) inhibitors derived from dl-piperazinecarboxylic acid has been described. The design involves: incorporation of hydroxamic acid as the bidentate chelating agent for catalytic Zn.sup.2.sup.+ , placement of a sulfonamide group at the 1N-position of the piperazine ring to fill the S1' pocket of the enzyme, and finally attachment of diverse functional groups at the 4N-position to optimize potency and peroral absorption. A unique combination of all three elements produced

inhibitor 20 with high affinity for **MMPs** 1, 3, 9, and 13 (24, 18, 1.9, and 1.3 nM, respectively). X-ray crystallography data obtained for **MMP-3** cocrystallized with 20 gave detailed information on key binding interactions defining an overall scaffold geometry for piperazine-based **MMP** inhibitors.

L51 ANSWER 73 OF 85 PASCAL COPYRIGHT 2005 INIST-CNRS. ALL RIGHTS RESERVED.  
on STN

ACCESSION NUMBER: 1999-0369021 PASCAL  
 COPYRIGHT NOTICE: Copyright .COPYRGT. 1999 INIST-CNRS. All rights reserved.  
 TITLE (IN ENGLISH): Picking the S.sub.1, S.sub.1' and S.sub.2' pockets of matrix metalloproteinases. A niche for potent acyclic sulfonamide inhibitors  
 AUTHOR: HANESSIAN S.; BOUZBOUZ S.; BOUDON A.; TUCKER G. C.; PEYROULAN D.  
 CORPORATE SOURCE: Department of Chemistry, Universite de Montreal, C.P. 6128, Succursale Centre-ville, Montreal, Quebec, H3C 3J7, Canada  
 SOURCE: Bioorganic & medicinal chemistry letters, (1999), 9(12), 1691-1696, 27 refs.  
 ISSN: 0960-894X  
 DOCUMENT TYPE: Journal  
 BIBLIOGRAPHIC LEVEL: Analytic  
 COUNTRY: United Kingdom  
 LANGUAGE: English  
 AVAILABILITY: INIST-22446, 354000085436970140  
 UP 20001101  
 AB A series of acyclic **hydroxamic** acids harboring strategically placed  $\alpha$ -arylsulfonamido and thioether groups was synthesized and found to be potent inhibitors of various **MMPs**. An unprecedented cleavage of t-butyl **hydroxamates** to **hydroxamic** acids was found.

L51 ANSWER 74 OF 85 PASCAL COPYRIGHT 2005 INIST-CNRS. ALL RIGHTS RESERVED.  
on STN

ACCESSION NUMBER: 1999-0217063 PASCAL  
 COPYRIGHT NOTICE: Copyright .COPYRGT. 1999 INIST-CNRS. All rights reserved.  
 TITLE (IN ENGLISH): Dual inhibition of phosphodiesterase 4 and matrix metalloproteinases by an (arylsulfonyl)**hydroxamic** acid template  
 AUTHOR: GRONEBERG R. D.; BURNS C. J.; MORRISSETTE M. M.; ULLRICH J. W.; MORRIS R. L.; DARBROUGH S.; DJURIC S. W.; CONDON S. M.; MCGEEHAN G. M.; LABAUDINIÈRE R.; NEUENSCHWANDER K.; SCOTESE A. C.; KLINE J. A.  
 CORPORATE SOURCE: Rhone-Poulenc Rorer, SW8, 500 Arcola Road, Collegeville, Pennsylvania 19426, United States  
 SOURCE: Journal of medicinal chemistry, (1999), 42(4), 541-544, 26 refs.  
 ISSN: 0022-2623 CODEN: JMCMAR  
 DOCUMENT TYPE: Journal; (letter to editor)  
 BIBLIOGRAPHIC LEVEL: Analytic  
 COUNTRY: United States  
 LANGUAGE: English  
 AVAILABILITY: INIST-9165, 354000074385190030  
 UP 20001101

L51 ANSWER 75 OF 85 PASCAL COPYRIGHT 2005 INIST-CNRS. ALL RIGHTS RESERVED.  
on STN

ACCESSION NUMBER: 1998-0119306 PASCAL  
 COPYRIGHT NOTICE: Copyright .COPYRGT. 1998 INIST-CNRS. All rights reserved.  
 TITLE (IN ENGLISH): Striking effect of **hydroxamic acid** substitution on the phosphodiesterase type 4 (PDE4) and **TNF.alpha.** inhibitory activity of two series of rolipram analogues : Implications for a new active site model of PDE4  
 AUTHOR: KLEINMAN E. F.; CAMPBELL E.; GIORDANO L. A.; COHAN V. L.; JENKINSON T. H.; CHENG J. B.; SHIRLEY J. T.; PETTIPHER E. R.; SALTER E. D.; HIBBS T. A.; DICAPUA F. M.; BORDNER J.  
 CORPORATE SOURCE: Central Research Division, Pfizer Inc., Groton, Connecticut 06340, United States  
 SOURCE: Journal of medicinal chemistry, (1998), 41(3), 266-270, 20 refs.  
 DOCUMENT TYPE: ISSN: 0022-2623 CODEN: JMCMAR  
 BIBLIOGRAPHIC LEVEL: Journal; (letter to editor)  
 COUNTRY: Analytic  
 LANGUAGE: English  
 AVAILABILITY: INIST-9165, 354000077888630020  
 UP 20001101

L51 ANSWER 76 OF 85 CANCERLIT on STN

ACCESSION NUMBER: 97302628 CANCERLIT  
 DOCUMENT NUMBER: 97302628 PubMed ID: 9158875  
 TITLE: Synthesis and biological evaluation of orally active **matrix metalloproteinase** inhibitors.  
 AUTHOR: Hirayama R; Yamamoto M; Tsukida T; Matsuo K; Obata Y; Sakamoto F; Ikeda S  
 CORPORATE SOURCE: New Drug Discovery Research Laboratory, Osaka, Japan.  
 SOURCE: BIOORGANIC AND MEDICINAL CHEMISTRY, (1997 Apr) 5 (4) 765-78.  
 Journal code: 9413298. ISSN: 0968-0896.  
 PUB. COUNTRY: ENGLAND: United Kingdom  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: MEDLINE; Priority Journals  
 OTHER SOURCE: MEDLINE 97302628  
 ENTRY MONTH: 199708  
 ENTRY DATE: Entered STN: 19970909  
 Last Updated on STN: 19970909  
 ED Entered STN: 19970909  
 Last Updated on STN: 19970909  
 AB The synthesis and biological evaluation of orally active inhibitors of **matrix metalloproteinase** are reported. Modifications of the P2' position and the alpha-substituent of **hydroxamic acid** derivatives were carried out, and revealed that the P2' substituent influenced the **MMP** inhibitory activities in vitro and in plasma after oral administration. The **hydroxamates** with **phenylglycine** at the P2' position were absorbed well orally. Compound 15e, which exhibited the longest duration of inhibitory activity in plasma after oral administration among the phenylglycine derivatives (5a-5d, 15a, 15c, 15e), was evaluated in a rat adjuvant arthritis model. A reduction in hind foot pad swelling and improvements of some inflammatory parameters were demonstrated when the compound was administered orally. These results indicate the potential of **MMP** inhibitors for rheumatoid arthritis.  
 CT Check Tags: Animal; Human; Male

Absorption  
 Administration, Oral  
 \*Anti-Inflammatory Agents: CS, chemical synthesis  
 Anti-Inflammatory Agents: PK, pharmacokinetics  
 Anti-Inflammatory Agents: TU, therapeutic use  
 \*Arthritis, Experimental: DT, drug therapy  
 Biological Availability  
 Collagenases: AI, antagonists & inhibitors  
 Collagenases: BL, blood  
 Disease Models, Animal  
 Gelatinases: AI, antagonists & inhibitors  
 Gelatinases: BL, blood  
 Hindlimb: DE, drug effects  
**Hydroxamic Acids: CH, chemistry**  
 \*Metalloendopeptidases: AI, antagonists & inhibitors  
 Mice  
 \*Protease Inhibitors: CS, chemical synthesis  
 Protease Inhibitors: PK, pharmacokinetics  
 Protease Inhibitors: TU, therapeutic use  
 Rats  
 Rats, Inbred Lew  
 Solubility  
 Structure-Activity Relationship  
 Tumor Cells, Cultured  
 CN 0 (Anti-Inflammatory Agents); 0 (Hydroxamic Acids); 0 (Protease Inhibitors); EC 3.4.24 (Metalloendopeptidases); EC 3.4.24.- (Collagenases); EC 3.4.24.- (Gelatinases)

L51 ANSWER 77 OF 85 DRUGU COPYRIGHT 2005 THE THOMSON CORP on STN  
 ACCESSION NUMBER: 2000-35901 DRUGU C P B  
 TITLE: Novel 4-substituted phenylsulfanyl alkyl and aryl hydroxamic acid TACE and MMP inhibitors.  
 AUTHOR: Davis J M; Venkatesan A; Baker J L; Grosu G T; Ellingboe J W; Zask A; Skotnicki J; Killar L; Cowling R; Jin G  
 CORPORATE SOURCE: Wyeth-Ayerst  
 LOCATION: Pearl River, N.Y., USA  
 SOURCE: Abstr.Pap.Am.Chem.Soc. (219 Meet., Pt. 2, MEDI 281, 2000)-1  
 Fig. CODEN: ACSRAL ISSN: 0065-7727  
 AVAIL. OF DOC.: Chemical Sciences, Wyeth-Ayerst Research, 401 N. Middletown Road, Pearl River, NY 10965, U.S.A. (email: davisjm@war.wyeth.com). (12 authors).  
 LANGUAGE: English  
 DOCUMENT TYPE: Journal  
 FIELD AVAIL.: AB; LA; CT  
 FILE SEGMENT: Literature  
 AB Tumor necrosis factor alpha (TNFa) converting enzyme (TACE) plays a key role in the release of TNFa, a cytokine involved in inflammation, from cells. Unregulated, this can lead to several pathological conditions including rheumatoid arthritis. Several sulfanyl hydroxamic acids of structure (I) were synthesized and evaluated for inhibition of TACE and the related matrix metalloproteinase (MMP) 1, 9 and 13 in-vitro. No further details are given. (conference abstract: 219th ACS National Meeting, San Francisco, California, USA, 2000).

L51 ANSWER 78 OF 85 DRUGU COPYRIGHT 2005 THE THOMSON CORP on STN  
 ACCESSION NUMBER: 1999-02274 DRUGU C P B

TITLE: **Hydroxamate derivatives of substrate-analogous peptides containing aminomalonic acid are potent inhibitors of matrix metalloproteinases.**  
 AUTHOR: Krumme D; Wenzel H; Tschesche H  
 CORPORATE SOURCE: Univ.Bielefeld  
 LOCATION: Bielefeld, Ger.  
 SOURCE: FEBS Lett. (436, No. 2, 209-12, 1998) 1 Fig. 1 Tab. 16 Ref.  
 CODEN: FEBLAL ISSN: 0014-5793  
 AVAIL. OF DOC.: Universitaet Bielefeld, Fakultaet fuer Chemie, Abteilung Biochemie I, Universitaetsstrasse 25, D-33615 Bielefeld, Germany. (H.T.). (e-mail: harald.tschesche@uni-bielefeld.de).  
 LANGUAGE: English  
 DOCUMENT TYPE: Journal  
 FIELD AVAIL.: AB; LA; CT  
 FILE SEGMENT: Literature

AB Tetrapeptides Boc-Pro-Aaa-Ama(NHOH)-Tyr(Bzl)-R2 were prepared, where Aaa = Gly, Ala or Leu, Ama(NHOH) = aminomalonic acid **hydroxamate**, Tyr(Bzl) = O-benzyl-Tyr, and R2 = bulky amine. Peptides were tested as **matrix metalloproteinase (MMP)** human gelatinase-B (**MMP-9**) inhibitors. Analogs had **MMP-9** selectivity and were weak inhibitors of the catalytic domain of neutrophil elastase (cdMMP-8). The peptides resisted proteinase cleavage. Substrate was (7-methoxycoumarin-4-yl)acetyl Pro-Leu-Gly-Leu (3-(2,4-dinitrophenyl) L-2,3-diaminopropionyl)-Ala-Arg-NH2 which was cleaved at the Gly-Leu bond by both cdMMP-8 and **MMP-9**.

L51 ANSWER 79 OF 85 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 2005:432055 SCISEARCH  
 THE GENUINE ARTICLE: 916HS  
 TITLE: Conformational variability of **matrix metalloproteinases**: Beyond a single 3D structure  
 AUTHOR: Bertini I (Reprint); Calderone V; Cosenza M; Fragai M; Lee Y M; Luchinat C; Mangani S; Terni B; Turano P  
 CORPORATE SOURCE: Univ Florence, Magnet Resonance Ctr, Via Luigi Sacconi 6, I-50019 Sesto Fiorentino, Italy (Reprint); Univ Florence, Magnet Resonance Ctr, I-50019 Sesto Fiorentino, Italy; Univ Florence, Dept Chem, I-50019 Sesto Fiorentino, Italy; Univ Siena, Dept Chem, I-53100 Siena, Italy; Univ Florence, Dept Agr Biotechnol, I-50144 Florence, Italy bertini@cerm.unifi.it  
 COUNTRY OF AUTHOR: Italy  
 SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (12 APR 2005) Vol. 102, No. 15, pp. 5334-5339.  
 ISSN: 0027-8424.  
 PUBLISHER: NATL ACAD SCIENCES, 2101 CONSTITUTION AVE NW, WASHINGTON, DC 20418 USA.  
 DOCUMENT TYPE: Article; Journal  
 LANGUAGE: English  
 REFERENCE COUNT: 34  
 ENTRY DATE: Entered STN: 28 Apr 2005  
 Last Updated on STN: 28 Apr 2005  
 \*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*

ED Entered STN: 28 Apr 2005  
 Last Updated on STN: 28 Apr 2005

AB The structures of the catalytic domain of **matrix metalloproteinase 12** in the presence of **acetohydroxamic acid** and **N-isobutyl-N-[4-methoxyphenylsulfonyl]glycyl hydroxamic acid** have been solved by x-ray diffraction in the

crystalline state at 1.0 and 1.3-angstrom resolution, respectively, and compared with the previously published x-ray structure at 1.2-angstrom resolution of the adduct with batimastat. The structure of the N-isobutyl-N-[4-methoxyphenylsulfonyl]glycyl hydroxamic acid adduct has been solved by NMR in solution. The three x-ray structures and the solution structure are similar but not identical to one another, the differences being sizably higher in the loops. We propose that many of the loops show a dynamical behavior in solution on a variety of time scales. Different conformations of some flexible regions of the protein can be observed as "frozen" in different crystalline environments. The mobility in solution studied by NMR reveals conformational equilibria in accessible time scales, i.e., from 10(-5) s to ms and more. Averaging of some residual dipolar couplings is consistent with further motions down to 10(-9) s. Finally, local thermal motions of each frozen conformation in the crystalline state at 100 K correlate well with local motions on the picosecond time scale. Flexibility/conformational heterogeneity in crucial parts of the catalytic domain is a rule rather than an exception in matrix metalloproteinases, and its extent may be underestimated by inspection of one x-ray structure. Backbone flexibility may play a role in the difficulties encountered in the design of selective inhibitors, whereas it may be a requisite for substrate binding and broad substrate specificity.

L51 ANSWER 80 OF 85 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN  
 ACCESSION NUMBER: 2005:525729 SCISEARCH  
 THE GENUINE ARTICLE: 927OU  
 TITLE: Synthesis, radiosynthesis, in vitro and preliminary in vivo evaluation of biphenyl carboxylic and hydroxamic matrix metalloproteinase (MMP) inhibitors as potential tumor imaging agents  
 AUTHOR: Oltenfreiter R (Reprint); Staelens L; Hillaert U; Heremans A; Noel A; Frankenmeier F; Slegers G  
 CORPORATE SOURCE: State Univ Ghent, Lab Radiopharm, Harelbekestr 72, B-9000 Ghent, Belgium (Reprint); State Univ Ghent, Lab Radiopharm, B-9000 Ghent, Belgium; Univ Liege, Lab Tumor & Dev Biol, Liege, Belgium; State Univ Ghent, Med Chem Lab, B-9000 Ghent, Belgium  
 COUNTRY OF AUTHOR: Belgium  
 SOURCE: APPLIED RADIATION AND ISOTOPES, (JUN 2005) Vol. 62, No. 6, pp. 903-913.  
 ISSN: 0969-8043.  
 PUBLISHER: PERGAMON-ELSEVIER SCIENCE LTD, THE BOULEVARD, LANGFORD LANE, KIDLINGTON, OXFORD OX5 1GB, ENGLAND.  
 DOCUMENT TYPE: Article; Journal  
 LANGUAGE: English  
 REFERENCE COUNT: 30  
 ENTRY DATE: Entered STN: 2 Jun 2005  
 Last Updated on STN: 2 Jun 2005  
 \*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*  
 ED Entered STN: 2 Jun 2005  
 Last Updated on STN: 2 Jun 2005  
 AB Excess matrix degradation is one of the hallmarks of cancer and is an important factor in the process of tumor progression. It is implicated in invasion, metastasis, growth, angiogenesis and migration. Many characteristics of matrix metalloproteinases (MMPs) make them attractive therapeutic and diagnostic targets. MMP expression is upregulated at the tumor site, with localization of activity in the

tumor or the surrounding stroma, providing a target for medical imaging techniques. Radioiodinated carboxylic and **hydroxamic** **MMP** inhibitors 2-(4'-(<sup>123</sup>I)) iodo-biphenyl-4-sulfonylamino)-3-methyl-butyric acid (9) and 2-(4'-(I-123) iodo-biphenyl-4-sulfonylamino)-3-methyl-butyramide (11), their unlabelled standards and precursors were synthesized. Radioiodination was conducted by electrophilic aromatic substitution of the tributylstannyl precursors and resulted in radiochemical yields of 70 +/- 5% (n = 6) and 60 + 5% (n = 4), respectively. In vitro zymography and enzyme assays showed for both **hydroxamic** acid and carboxylic acid compounds a good inhibition activity and a high selectivity for **MMP-2**. In vivo biodistribution in NMRI mice showed no long-term accumulation in organs and the possibility to accumulate in the tumor in a later phase of this study. (c) 2005 Elsevier Ltd. All rights reserved.

L51 ANSWER 81 OF 85 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 2003:960039 SCISEARCH

THE GENUINE ARTICLE: 737PA

TITLE: Iminodiacyl-**hydroxamate** derivatives as metalloproteinase inhibitors: equilibrium complexation studies with Cu(II), Zn(II) and Ni(II)

AUTHOR: Chaves S; Marques S; Santos M A (Reprint)

CORPORATE SOURCE: Inst Super Tecn, Ctr Quim Estrutural, Complexo 1, Av Rovisco Pais, P-1049001 Lisbon, Portugal (Reprint); Inst Super Tecn, Ctr Quim Estrutural, P-1049001 Lisbon, Portugal

COUNTRY OF AUTHOR: Portugal

SOURCE: JOURNAL OF INORGANIC BIOCHEMISTRY, (1 DEC 2003) Vol. 97, No. 4, pp. 345-353.

ISSN: 0162-0134.

PUBLISHER: ELSEVIER SCIENCE INC, 360 PARK AVE SOUTH, NEW YORK, NY 10010-1710 USA.

DOCUMENT TYPE: Article; Journal

LANGUAGE: English

REFERENCE COUNT: 48

ENTRY DATE: Entered STN: 14 Nov 2003

Last Updated on STN: 14 Nov 2003

\*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*

ED Entered STN: 14 Nov 2003

Last Updated on STN: 14 Nov 2003

AB Two new iminodiacyl-**hydroxamate** derivatives, the N-**benzyl**-N-carboxymethyl-iminoacetohydroxamic acid (H2L1) and the N-**benzyl**-N'-hydroxypiperazine-2,6-dione (HL2), have been recently reported as very effective inhibitors against a set of zinc-containing **matrix metalloproteinases** (**MMPs**). Herein, aimed at understanding that inhibitory function, these compounds are studied in their complex formation equilibria with three biologically relevant first-row transition M2+ metal ions (M=Cu, Zn, Ni) by using potentiometric and spectroscopic techniques. At physiological conditions, complexation of these metal ions by H2L1 mostly occurs with formation of 1:1 species by tridentate co-ordination (O,N,N) (carboxylate-amino-hydroxamate), whereas complexation with HL2 mainly involves the formation of 1:2 (M:L) species with normal (O,O) hydroxamate coordination. Moreover, at higher pH, H2L1 is able to form a pentanuclear tetrameric copper complex with an interesting 12-metallacrown-4 structure. (C) 2003 Elsevier Inc. All rights reserved.

L51 ANSWER 82 OF 85 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 2002:55980 SCISEARCH  
 THE GENUINE ARTICLE: 508KZ  
 TITLE: **Phenoxyphenyl sulfone N-formylhydroxylamines (retrohydroxamates) as potent, selective, orally bioavailable matrix metalloproteinase inhibitors**  
 AUTHOR: Wada C K (Reprint); Holms J H; Curtin M L; Dai Y; Florjancic A S; Garland R B; Guo Y; Heyman H R; Stacey J R; Steinman D H; Albert D H; Bouska J J; Elmore I N; Goodfellow C L; Marcotte P A; Tapang P; Morgan D W; Michaelides M R; Davidsen S K  
 CORPORATE SOURCE: Abbott Labs, Canc Res Area, Dept 47J, Bldg AP10, 100 Abbott Pk Rd, Abbott Pk, IL 60064 USA (Reprint); Abbott Labs, Canc Res Area, Dept 47J, Abbott Pk, IL 60064 USA  
 COUNTRY OF AUTHOR: USA  
 SOURCE: JOURNAL OF MEDICINAL CHEMISTRY, (3 JAN 2002) Vol. 45, No. 1, pp. 219-232.  
 ISSN: 0022-2623.  
 PUBLISHER: AMER CHEMICAL SOC, 1155 16TH ST, NW, WASHINGTON, DC 20036 USA.  
 DOCUMENT TYPE: Article; Journal  
 LANGUAGE: English  
 REFERENCE COUNT: 31  
 ENTRY DATE: Entered STN: 25 Jan 2002  
 Last Updated on STN: 25 Jan 2002  
 \*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*

ED    Entered STN: 25 Jan 2002  
 Last Updated on STN: 25 Jan 2002

AB    A novel series of sulfone N-formylhydroxylamines (retrohydroxamates) have been investigated as **matrix metalloproteinases (MMP)** inhibitors. The substitution of the ether linkage of ABT-770 (5) with a sulfone group 13a led to a substantial increase in activity against **MMP-9** but was accompanied by a loss of selectivity for inhibition of **MMP-2** and -9 over **MMP-1** and diminished oral exposure. Replacement of the biphenyl P1' substituent with a phenoxyphenyl group provided compounds that are highly selective for inhibition of **MMP-2** and -9 over **MMP-1**. Optimization of the substituent adjacent to the **retrohydroxamate** center in this series led to the clinical candidate ABT-518 (6), a highly potent, selective, orally bioavailable **MMP** inhibitor that has been shown to significantly inhibit tumor growth in animal cancer models.

L51 ANSWER 83 OF 85 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 2000:290351 SCISEARCH  
 THE GENUINE ARTICLE: 302XH  
 TITLE: Protease inhibitors - Part 5. Alkyl/arylsulfonyl- and arylsulfonylureido-/arylureido- glycine hydroxamate inhibitors of Clostridium histolyticum collagenase  
 AUTHOR: Scozzafava A; Supuran C T (Reprint)  
 CORPORATE SOURCE: Univ Florence, Lab Chim Inorgan & Bioinorgan, Via Gino Capponi 7, I-50121 Florence, Italy (Reprint); Univ Florence, Lab Chim Inorgan & Bioinorgan, I-50121 Florence, Italy  
 COUNTRY OF AUTHOR: Italy  
 SOURCE: EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, (MAR 2000) Vol. 35, No. 3, pp. 299-307.  
 ISSN: 0223-5234.

PUBLISHER: EDITIONS SCIENTIFIQUES MEDICALES ELSEVIER, 23 RUE LINOIS,  
75724 PARIS CEDEX 15, FRANCE.  
 DOCUMENT TYPE: Article; Journal  
 LANGUAGE: English  
 REFERENCE COUNT: 49  
 ENTRY DATE: Entered STN: 2000  
                  Last Updated on STN: 2000  
 \*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*

ED   Entered STN: 2000  
      Last Updated on STN: 2000  
 AB   Reaction of alkyl/arylsulfonyl halides with glycine afforded a series of derivatives which were first N-benzylated by treatment with benzyl chloride, and then converted to the corresponding hydroxamic acids with hydroxylamine in the presence of carbodiimide derivatives. Other derivatives were obtained by reaction of N-benzyl-glycine with aryl isocyanates, arylsulfonyl isocyanates or benzoyl isothiocyanate, followed by conversion of their COOH group into the CONHOH moiety, as mentioned above. The 90 new compounds reported here were assayed as inhibitors of the Clostridium histolyticum collagenase (EC 3.4.24.3), a zinc enzyme which degrades triple helical regions of native collagen. The prepared hydroxamate derivatives were generally 100-500 times more active than the corresponding carboxylates. In the series of synthesized hydroxamates, substitution patterns leading to the best inhibitors were those involving perfluoroalkylsulfonyl- and substituted-arylsulfonyl moieties, such as pentafluorophenylsulfonyl, 3- and 4-carboxyphenylsulfonyl-, 3-trifluoromethyl-phenylsulfonyl or 1- and 2-naphthyl among others. Thus, it seems that similarly to the matrix metalloproteinase (MMP) hydroxamate inhibitors, Clostridium histolyticum collagenase inhibitors should incorporate hydrophobic moieties at the P-1- and P-2-sites, whereas the alpha-carbon substituent may be a small and compact moiety (such as H, for the Gly derivatives reported here). Such compounds might lead to the design of collagenase inhibitor-based drugs useful as anti-cancer, anti-arthritis or anti-bacterial agents for the treatment of corneal keratitis. (C) 2000 Editions scientifiques et medicales Elsevier SAS.

L51 ANSWER 84 OF 85 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN  
 ACCESSION NUMBER: 2000:749562 SCISEARCH  
 THE GENUINE ARTICLE: 317UW  
 TITLE: Novel 4-substituted phenylsulfanyl alkyl and aryl hydroxamic acid TACE and MMP inhibitors.  
 AUTHOR: Davis J M (Reprint); Venkatesan A; Baker J L; Grosu G T; Ellingboe J W; Zask A; Skotnicki J; Killar L; Cowling R; Jin G X; Sharr M; Sung A  
 CORPORATE SOURCE: Wyeth Ayerst Res, Chem Sci, Pearl River, NY 10965 USA;  
                   Wyeth Ayerst Res, Oncol Immunoinflammatory Dis, Pearl River, NY 10965 USA  
 COUNTRY OF AUTHOR: USA  
 SOURCE: ABSTRACTS OF PAPERS OF THE AMERICAN CHEMICAL SOCIETY, (26 MAR 2000) Vol. 219, Part 2, pp. U52-U52. MA 281-MEDI.  
                   ISSN: 0065-7727.  
 PUBLISHER: AMER CHEMICAL SOC, 1155 16TH ST, NW, WASHINGTON, DC 20036 USA.  
 DOCUMENT TYPE: Conference; Journal  
 LANGUAGE: English  
 REFERENCE COUNT: 0  
 ENTRY DATE: Entered STN: 2000

Last Updated on STN: 2000

ED    Entered STN: 2000

Last Updated on STN: 2000

L51 ANSWER 85 OF 85 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on  
STN

ACCESSION NUMBER: 1999:682758 SCISEARCH

THE GENUINE ARTICLE: 232MG

TITLE: Arylsulphonamide hydroxamic acids as potent  
inhibitors of MMP-13

AUTHOR: ANON

SOURCE: EXPERT OPINION ON THERAPEUTIC PATENTS, (SEP 1999) Vol. 9,  
No. 9, pp. 1303-1307.

ISSN: 1354-3776.

PUBLISHER: ASHLEY PUBLICATIONS LTD, UNITEC HOUSE, 3RD FL, 2 ALBERT  
PLACE FINCHLEY CENTRAL, LONDON N3 1QB, ENGLAND.

DOCUMENT TYPE: Article; Journal

LANGUAGE: English

REFERENCE COUNT: 19

ENTRY DATE: Entered STN: 1999

Last Updated on STN: 1999

\*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*

ED    Entered STN: 1999

Last Updated on STN: 1999

AB    Pfizer has disclosed a series of phenoxyphenyl sulphonamide  
hydroxamic acids, containing Ca gem-disubstitution and a novel  
N-ethylcarboxylate moiety, which are potent inhibitors of matrix  
metalloproteinase-13 (MMP-13), an enzyme which has been  
implicated in such disease states as cancer and arthritis. The compounds  
are significantly selective (300-1000 fold) for MMP-13 versus  
MMP-1, the inhibition of which is believed to be associated with  
clinical side effects with previous broad spectrum MMP  
inhibitors. The Pfizer compounds are equally or more selective than  
several current clinical candidates and may have favourable  
pharmacodynamic profiles.

=> d his 150

(FILE 'HCAPLUS, MEDLINE, BIOSIS, EMBASE, PASCAL, JICST-EPLUS, CABA, CANCERLIT, DRUGU, SCISEARCH, WPIX, CONF, CONFSCI, DISSABS' ENTERED AT 08:28:53 ON 13 OCT 2005)

L50 10 DUP REM L49 (3 DUPLICATES REMOVED)

=> d que 150

L1 QUE ABB=ON PLU=ON ?HYDANTOI? OR ?HYDROXAM?  
 L48 147 SEA MADUSKUIE, T?/AU  
 L49 13 SEA L48 AND L1  
 L50 10 DUP REM L49 (3 DUPLICATES REMOVED)

=> d ibib ed ab 150 1-10

YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS, BIOSIS, DRUGU, SCISEARCH' - CONTINUE?  
 (Y)/N:y

L50 ANSWER 1 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 1

ACCESSION NUMBER: 2004:120672 HCAPLUS

DOCUMENT NUMBER: 140:177322

TITLE: **Hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNF $\alpha$  converting enzyme for use in treatment of diseases**

INVENTOR(S): **Maduskuie, Thomas P.**

PATENT ASSIGNEE(S): Bristol-Myers Squibb Company, USA

SOURCE: PCT Int. Appl., 81 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004012663	A2	20040212	WO 2003-US23989	20030731
WO 2004012663	A3	20040708		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004063698	A1	20040401	US 2003-632197	20030731
PRIORITY APPLN. INFO.:			US 2002-400237P	P 20020801

OTHER SOURCE(S): MARPAT 140:177322

ED Entered STN: 13 Feb 2004

AB MMP or TACE-inhibiting hydroxamic acid derivs. for use in treatment of diseases are disclosed. Thus, 3,N-dihydroxy-2,2-dimethyl-3-[6-(2-methylquinolin-4-ylmethoxy)naphthalen-2-yl]propionamide (I), 4,N-dihydroxy-4-[4-(2-methylquinolin-4-ylmethoxy)phenyl]butyramide (II), N-Hydroxy-2-{2-[4-(2-methylquinolin-4-ylmethoxy)phenyl]tetrahydrofuran-2-yl}acetamide (III), and 3,N-dihydroxy-3-(6-methoxynaphthalen-2-yl)-2,2-dimethylpropionamide (IV) as well as 23 other compds. were synthesized and

tested as MMP inhibitors. Some of these compds. inhibited MMPs with Ki's ≤ 10 μM.

L50 ANSWER 2 OF 10 HCPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 2  
 ACCESSION NUMBER: 2003:634809 HCPLUS  
 TITLE: Design, synthesis and evaluation of β-amino hydroxamic acids as selective tumor necrosis factor-α converting enzyme inhibitors  
 AUTHOR(S): Duan, James J.-W.; Ott, Gregory R.; King, Bryan W.; Maduskuie, Thomas P.; Xue, Chu-Biao; Chen, Lihua; Lu, Zhonghui; Gilmore, John L.; Asakawa, Naoyuki; Mercer, Stephen E.; Xu, Meizhong; Harris, Cathy M.; Wasserman, Zelda R.; Liu, Rui-Qin; Covington, Maryanne B.; Qian, Mingxin; Vaddi, Krishna G.; Christ, David D.; Hardman, Karl D.; Ribadeneira, Maria D.; Newton, Robert C.; Trzaskos, James M.; Decicco, Carl P.  
 CORPORATE SOURCE: Discovery Chemistry, Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ, 08543-4000, USA  
 SOURCE: Abstracts of Papers, 226th ACS National Meeting, New York, NY, United States, September 7-11, 2003 (2003), MEDI-201. American Chemical Society: Washington, D.C.  
 CODEN: 69EKY9  
 DOCUMENT TYPE: Conference; Meeting Abstract  
 LANGUAGE: English  
 ED Entered STN: 15 Aug 2003  
 AB Tumor necrosis factor-α converting enzyme (TACE) is the principal metalloprotease that processes the pro-form of tumor necrosis factor-α (TNFα) to the soluble form. With the clin. success of anti-TNFα biologics in diseases such as rheumatoid arthritis, TACE has attracted significant interest as an intervention point for small mols. to suppress the amount of circulating TNFα. Most of the early TACE inhibitors were derived from inhibitors of structurally related matrix metalloproteinases (MMPs) and hence suffered from lack of TACE selectivity. In an effort to discover selective TACE inhibitors, a series of β-amino hydroxamates was found to be highly potent and selective for TACE relative to MMPs. The design, synthesis and evaluation of these inhibitors will be presented.

L50 ANSWER 3 OF 10 HCPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 3  
 ACCESSION NUMBER: 2000:117029 HCPLUS  
 DOCUMENT NUMBER: 132:166134  
 TITLE: Preparation of succinylaminoazepinones and related compounds as inhibitors of Aβ-peptide production.  
 INVENTOR(S): Olson, Richard E.; Maduskuie, Thomas P.; Thomas, Lorin Andrew  
 PATENT ASSIGNEE(S): Du Pont Pharmaceuticals Co., USA  
 SOURCE: PCT Int. Appl., 315 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 3  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000007995	A1	20000217	WO 1999-US17717	19990807
W: AL, AU, BR, CA, CN, CZ, EE, HU, IL, IN, JP, KR, LT, LV, MK, MX,				

NO, NZ, PL, RO, SG, SI, SK, TR, UA, VN, ZA, AM, AZ, BY, KG, KZ,  
 MD, RU, TJ, TM  
 RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,  
 PT, SE

HR 990246	A1	20000630	HR 1999-990246	19990806
CA 2338944	AA	20000217	CA 1999-2338944	19990807
AU 9953378	A1	20000228	AU 1999-53378	19990807
AU 756830	B2	20030123		
EP 1102752	A1	20010530	EP 1999-939010	19990807
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
TR 200100377	T2	20010621	TR 2001-200100377	19990807
BR 9912969	A	20010925	BR 1999-12969	19990807
NZ 509241	A	20030829	NZ 1999-509241	19990807
JP 2003526603	T2	20030909	JP 2000-563629	19990807
NZ 525513	A	20040924	NZ 1999-525513	19990807
PRIORITY APPLN. INFO.:				
			US 1998-95698P	P 19980807
			US 1998-113558P	P 19981224
			US 1999-120227P	P 19990215
			US 1999-370089	A 19990806
			US 1998-113588P	P 19981224
			WO 1999-US17717	W 19990807

OTHER SOURCE(S): MARPAT 132:166134

ED Entered STN: 18 Feb 2000

AB Title compds. [I; Q = OR1, NR1R2; R1 = H, (substituted) alkyl, alkenyl, carbocyclyl, aryl, heterocyclyl; R2 = H, NH2, OH, alkyl, alkoxy, PhO, PhCH2O, carbocyclyl, aryl, heterocyclyl; R3 = (CR7R7a)nR4, etc.; n = 0-3; R3a = H, OH, alkyl, alkoxy, alkenyloxy; R4 = H, OH, (substituted) alkyl, alkenyl, alkynyl, carbocyclyl, aryl, heterocyclyl; R5 = H, OR14, (substituted) alkyl, alkoxy, alkenyl, alkynyl, carbocyclyl, aryl, heterocyclyl; R14 = H, Ph, PhCH2, alkyl, alkoxyalkyl; R5a = H, OH, alkyl, alkoxy, alkenyl, alkenyloxy; R6 = H, (substituted) alkyl, carbocyclyl, aryl; R7, R7a = H, OH, Cl, F, Br, iodo, cyano, NO2, CF3, alkyl; W = (CR8R8a)p; p = 0-4; R8, R8a = H, F, alkyl, alkenyl, alkynyl, cycloalkyl; X = bond, (substituted) aryl, carbocyclyl, heterocyclyl; Y = bond, (CR9R9a)tV(CR9R9a)u; t, u = 0-3; R9, R9a = H, F, alkyl, cycloalkyl; V = bond, CO, O, S, SO, SO2, imino, etc.; Z = (substituted) alkyl, aryl, carbocyclyl, heterocyclyl; B = atoms to form an (unsatd.) (substituted) (heteroatom-containing) lactam ring], were prepared which inhibit the processing

of amyloid precursor protein and, more specifically, inhibit the production of A $\beta$ -peptide, thereby acting to prevent the formation of neurofibrillary deposits of amyloid protein. Thus, title compound (II) was prepared in several steps starting with L- $\alpha$ -amino- $\epsilon$ -caprolactam. I inhibited A $\beta$  production with IC50<100  $\mu$ M.

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L50 ANSWER 4 OF 10 HCPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2005:739801 HCPLUS

TITLE: Synthesis and structure-activity relationship of a novel, achiral series of TNF-alpha converting enzyme inhibitors

AUTHOR(S): Gilmore, John L.; King, Bryan W.; Harris, Cathy; Maduskuie, Thomas P.; Mercer, Stephen E.; Liu, Rui Quin; Covington, Maryanne B.; Qian, Mingxin; Ribadeneria, Maria D.; Vaddi, Krishna G.; Trzaskos, James M.; Newton, Robert C.; Decicco, Carl P.; Duan, James J.-W.

CORPORATE SOURCE: Discovery Chemistry, Bristol-Myers Squibb

SOURCE: Pharmaceutical Research Institute, Princeton, NJ,  
08543-4000, USA  
Abstracts of Papers, 230th ACS National Meeting,  
Washington, DC, United States, Aug. 28-Sept. 1, 2005  
(2005), MEDI-290. American Chemical Society:  
Washington, D. C.

DOCUMENT TYPE: Conference; Meeting Abstract; (computer optical disk)  
LANGUAGE: English

ED Entered STN: 12 Aug 2005

AB TNF-alpha is a potent proinflammatory cytokine which when disregulated has been implicated in chronic inflammatory diseases such as rheumatoid arthritis and Crohn's disease. The marketed anti-TNF biologics, Enbrel, Remicade, and Humira are effective in the treatment of these diseases by sequestering the soluble form of TNF-alpha. An alternate approach is to inhibit the release of soluble TNF-alpha via proteinase inhibitors such as TNF-alpha Converting Enzyme (TACE). We have discovered a novel, achiral series of compds. which are effective in inhibiting TACE. The synthesis and biol. activity of these beta, beta-cyclic beta-amidohydroxamic acids will be presented.

L50 ANSWER 5 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:772797 HCAPLUS

DOCUMENT NUMBER: 141:261062

TITLE: Preparation of (succinoylamino)azepinones as inhibitors of A<sub>B</sub> protein

INVENTOR(S): Olson, Richard E.; Maduskuie, Thomas P.;  
Thompson, Lorin Andrew

PATENT ASSIGNEE(S): Bristol-Myers Squibb Company, USA

SOURCE: U.S., 101 pp., Cont.-in-part of U.S. Ser. No. 370,089.

CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 3

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6794381	B1	20040921	US 2000-506360	20000217
HR 990246	A1	20000630	HR 1999-990246	19990806
TR 200100377	T2	20010621	TR 2001-200100377	19990807
NZ 525513	A	20040924	NZ 1999-525513	19990807
US 2003134841	A1	20030717	US 2002-285776	20021101
PRIORITY APPLN. INFO.:				
		US 1998-95698P	P	19980807
		US 1998-113558P	P	19981224
		US 1999-120227P	P	19990215
		US 1999-370089	A2	19990806
		US 2000-506360	A3	20000217

OTHER SOURCE(S): MARPAT 141:261062

ED Entered STN: 22 Sep 2004

AB The invention relates to aminoazepinones I [R<sub>1</sub> = H, (un)substituted alkyl, alkenyl, carbocyclyl, aryl or heterocyclyl; R<sub>2</sub> = H or alkyl; R<sub>3</sub> = (un)substituted (hetero)alkyl; R<sub>3a</sub> = H, OH, alkyl, alkoxy, alkenyloxy; R<sub>5</sub> = H, OH, (un)substituted alkyl, alkoxy, alkenyl, alkynyl, carbocyclyl, aryl or heterocyclyl; R<sub>5a</sub> = H, OH, alkyl, alkoxy, alkenyl, alkenyloxy; R<sub>6</sub> = H, (un)substituted alkyl, carbocyclyl or aryl; W = bond or (un)substituted alkylene; X = bond, (un)substituted aryl, carbocyclyl or heterocyclyl; Y = bond or (un)substituted (hetero)alkylene; Z = (un)substituted alkyl, aryl, carbocyclyl or heterocyclyl; B = atoms to form a saturated or unsatd. seven-membered ring which may be substituted]

which inhibit the processing of A $\beta$ -peptide, thereby acting to prevent the formation of neurof. deposits of amyloid protein. More particularly, the invention relates to the treatment of neurof. disorders related to  $\beta$ -amyloid production such as Alzheimer's disease and Down's Syndrome. Thus, aminoazepinone II was prepared in several steps starting with L- $\alpha$ -amino- $\epsilon$ -caprolactam. I inhibited A $\beta$  production with IC50 < 100  $\mu$ M.

REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L50 ANSWER 6 OF 10 HCPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:444499 HCPLUS

DOCUMENT NUMBER: 137:33207

TITLE: Preparation of novel N-substituted- $\gamma,\gamma$ -trisubstituted lactam derivatives as matrix metalloproteinase inhibitors

INVENTOR(S): Duan, Jingwu; DeCicco, Carl P.; Wasserman, Zelda R.; Maduskuie, Thomas P., Jr.

PATENT ASSIGNEE(S): USA

SOURCE: U.S., 119 pp.  
CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6403632	B1	20020611	US 2000-516709	20000301
US 2003134827	A1	20030717	US 2002-96619	20020312
US 6610731	B2	20030826		
PRIORITY APPLN. INFO.:			US 1997-62418P	P 19971003
			US 1998-165747	A3 19981002
			US 2000-516709	A3 20000301

OTHER SOURCE(S): MARPAT 137:33207

ED Entered STN: 13 Jun 2002

AB Title compds. [I; A is selected from COOH, CH<sub>2</sub>COOH, CONHOH, SH, CH<sub>2</sub>SH, PO(OH)<sub>2</sub>, etc.; ring B is a 4-8 membered cyclic amide containing 0-3 heteroatoms from O, N, and S, etc.; R1 is phenylmethoxyphenyl, phenoxyphenyl, etc.; R2 is H, CH<sub>3</sub>, Et, i-Pr, etc.; R1-R2 combine to form heterocyclic; R3 is H, alkylene, heterocyclic, etc.; R4 is H, alkylene, etc.; R3-R4 combine to form heterocyclic], stereoisomer, and pharmaceutically acceptable salt thereof are prepared as useful metalloprotease inhibitors. For instance, 4-benzyloxyphenyl acetate was sequentially alkylated (THF, NaHMDS) with MeI and allyl bromide to afford the  $\alpha,\alpha$ -bis(alkylated) derivative which was converted to the aldehyde (CH<sub>2</sub>Cl<sub>2</sub>, O<sub>3</sub>) and was subsequently reacted with D-alanine Me ester hydrochloride and Zn<sup>+</sup> in HOAc to yield the lactam ester. This intermediate was treated with hydroxylamine to give hydroxamic acid II.

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L50 ANSWER 7 OF 10 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 2004:2000 BIOSIS

DOCUMENT NUMBER: PREV200400003348

TITLE: Design, synthesis and evaluation of beta-amino hydroxamic acids as selective tumor necrosis factor-alpha converting enzyme inhibitors.

AUTHOR(S): Duan, James J.-W. [Reprint Author]; Ott, Gregory R.

[Reprint Author]; King, Bryan W. [Reprint Author];  
**Maduskuie, Thomas P.** [Reprint Author]; Xue,  
 Chu-Biao [Reprint Author]; Chen, Lihua [Reprint Author];  
 Lu, Zhonghui [Reprint Author]; Gilmore, John L. [Reprint  
 Author]; Asakawa, Naoyuki [Reprint Author]; Mercer, Stephen  
 E. [Reprint Author]; Xu, Meizhong [Reprint Author]; Harris,  
 Cathy M. [Reprint Author]; Wasserman, Zelda R. [Reprint  
 Author]; Liu, Rui-Qin [Reprint Author]; Covington, Maryanne  
 B. [Reprint Author]; Qian, MingXin [Reprint Author]; Vaddi,  
 Krishna G. [Reprint Author]; Christ, David D. [Reprint  
 Author]; Hardman, Karl D. [Reprint Author]; Ribadeneira,  
 Maria D. [Reprint Author]; Newton, Robert C. [Reprint  
 Author]; Trzaskos, James M. [Reprint Author]; Decicco, Carl  
 P. [Reprint Author]

**CORPORATE SOURCE:** Discovery Chemistry, Bristol-Myers Squibb Pharmaceutical Research Institute, P.O. Box 4000, Princeton, NJ, 08543-4000, USA  
 james.duan@bms.com

**SOURCE:** Abstracts of Papers American Chemical Society, (2003) Vol. 226, No. 1-2, pp. MED1 201. print.  
 Meeting Info.: 226th ACS (American Chemical Society)  
 National Meeting. New York, NY, USA. September 07-11, 2003.  
 American Chemical Society.  
 ISSN: 0065-7727 (ISSN print).

**DOCUMENT TYPE:** Conference; (Meeting)  
 Conference; Abstract; (Meeting Abstract)

**LANGUAGE:** English

**ENTRY DATE:** Entered STN: 17 Dec 2003  
 Last Updated on STN: 17 Dec 2003

**ED** Entered STN: 17 Dec 2003  
 Last Updated on STN: 17 Dec 2003

L50 ANSWER 8 OF 10 DRUGU COPYRIGHT 2005 THE THOMSON CORP on STN  
 ACCESSION NUMBER: 1995-12212 DRUGU C P B  
**TITLE:** Acyl CoA: Cholesterol acyltransferase (ACAT) inhibitors:  
 ureas bearing heterocyclic groups biosteric for an imidazole.  
**AUTHOR:** Wilde R G; Billheimer J T; Germain S J; Gillies P J; Higley C  
 A; Kezar H S III; **Maduskuie T P**; Shimshick E S;  
 Wexler R R

**CORPORATE SOURCE:** Du-Pont; Merck-USA

**LOCATION:** Wilmington, Del., USA  
**SOURCE:** ; Bioorg.Med.Chem.Lett. (5, No. 2, 167-72, 1995) 4 Fig. 3

Tab. 10 Ref.

**CODEN:** ; BMCL

**AVAIL. OF DOC.:** Cardiovascular Diseases Research, Division of Research and Development, The DuPont Merck Pharmaceutical Company, DuPont Experimental Station, Wilmington, Delaware, U.S.A.  
 19880-0353.

**LANGUAGE:** English

**DOCUMENT TYPE:** Journal

**FIELD AVAIL.:** AB; LA; CT

**FILE SEGMENT:** Literature

**AB** A series of compounds (1-34) bearing heterocyclic substituents was synthesized and evaluated in-vitro for inhibition of acyl CoA: cholesterol acyltransferase (ACAT) using two assays (one based on the determination of the formation of labeled cholestryloleate in the presence of rat hepatic microsomes; the second was based on the measurement of the formation of cholestryloleate (CE) by following the rate of oleate incorporation into CE). Results obtained indicated that for five-membered rings fused to another ring, the most potent inhibitors

of ACAT were imidazoles. Oxazoles, thiazoles and N-substituted imidazoles were less potent. Triazoles were also less potent, but the hydantoin compound (33) was within one order of magnitude of DuP 128. From results of QSAR, extremely hydrophilic heterocycles were expected to decrease potency.

L50 ANSWER 9 OF 10 DRUGU COPYRIGHT 2005 THE THOMSON CORP on STN  
 ACCESSION NUMBER: 1989-22660 DRUGU C P  
 TITLE: Hydroxyacetophenone- Derived Antagonists of the Peptidoleukotrienes.  
 AUTHOR: Brown F J; Bernstein P R; Cronk L A; Dosset D L; Hebbel K C; Maduskuie T P  
 CORPORATE SOURCE: ICI-Americas  
 LOCATION: Wilmington, Delaware, United States  
 SOURCE: J.Med.Chem. (32, No. 4, 807-26, 1989) 9 Tab. 50 Ref.  
 CODEN: JMCMAR ISSN: 0022-2623  
 AVAIL. OF DOC.: Department of Medicinal Chemistry, ICI Pharmaceuticals Group, Wilmington, Delaware 19897, U.S.A. (12 authors).  
 LANGUAGE: English  
 DOCUMENT TYPE: Journal  
 FIELD AVAIL.: AB; LA; CT; MPC  
 FILE SEGMENT: Literature  
 AB Based on the possible similarities between LTD4 and its prototypical antagonist FPL-55712, a series of LT antagonists was prepared incorporating a hydroxyacetophenone moiety. They were tested as LTD4 and LTE4 antagonists in vitro using guinea pig trachea (GPT) and selected compounds were tested i.p. against aerosol LTD4 challenge in guinea pigs. FPL-55712 and LY-171883 were used as standards. Structure-activity relationships were evaluated.

L50 ANSWER 10 OF 10 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN  
 ACCESSION NUMBER: 2004:179764 SCISEARCH  
 THE GENUINE ARTICLE: 751JG  
 TITLE: Design, synthesis and evaluation of beta-amino hydroxamic acids as selective tumor necrosis factor-alpha converting enzyme inhibitors.  
 AUTHOR: Duan J J W (Reprint); Ott G R; King B W; Maduskuie T P; Xue C B; Chen L H; Lu Z H; Gilmore J L; Asakawa N; Mercer S E; Xu M Z; Harris C M; Wasserman Z R; Liu R Q; Covington M B; Qian M X; Vaddi K G; Christ D D; Hardman K D; Ribadeneira M D; Newton R C; Trzaskos J M; Decicco C P  
 CORPORATE SOURCE: Bristol Myers Squibb Co, Pharmaceut Res Inst, Discovery Chem, Princeton, NJ 08543 USA  
 COUNTRY OF AUTHOR: USA  
 SOURCE: ABSTRACTS OF PAPERS OF THE AMERICAN CHEMICAL SOCIETY, (SEP 2003) Vol. 226, Part 2, pp. U38-U38. MA 201-MEDI.  
 ISSN: 0065-7727.  
 PUBLISHER: AMER CHEMICAL SOC, 1155 16TH ST, NW, WASHINGTON, DC 20036 USA.  
 DOCUMENT TYPE: Conference; Journal  
 LANGUAGE: English  
 REFERENCE COUNT: 0  
 ENTRY DATE: Entered STN: 5 Mar 2004  
 Last Updated on STN: 5 Mar 2004  
 ED Entered STN: 5 Mar 2004  
 Last Updated on STN: 5 Mar 2004

=> file stnguide

Hoffman 10/632,197

10/13/2005

FILE 'STNGUIDE' ENTERED AT 08:37:18 ON 13 OCT 2005  
USE IS SUBJECT TO THE TERMS OF YOUR CUSTOMER AGREEMENT  
COPYRIGHT (C) 2005 AMERICAN CHEMICAL SOCIETY, JAPAN SCIENCE  
AND TECHNOLOGY CORPORATION, AND FACHINFORMATIONSZENTRUM KARLSRUHE

FILE CONTAINS CURRENT INFORMATION.  
LAST RELOADED: Oct 7, 2005 (20051007/UP).

=>



4/4

Hoffman 10/632,197

10/13/2005

=> (d his ful)

(FILE 'HOME' ENTERED AT 10:09:25 ON 11 OCT 2005)

FILE 'ZCPLUS' ENTERED AT 10:09:33 ON 11 OCT 2005  
E US2003-632197/APPS

L1 FILE 'HCAPLUS' ENTERED AT 10:09:56 ON 11 OCT 2005  
1 SEA ABB=ON PLU=ON US2003-632197/APPS  
SAVE TEMP L1 HOF197HCAAPP/A

FILE 'STNGUIDE' ENTERED AT 10:10:14 ON 11 OCT 2005

FILE 'HCAPLUS' ENTERED AT 10:10:27 ON 11 OCT 2005  
D IBIB ED AB IND

FILE 'STNGUIDE' ENTERED AT 10:10:28 ON 11 OCT 2005

L2 FILE 'WPIX' ENTERED AT 10:12:02 ON 11 OCT 2005  
1 SEA ABB=ON PLU=ON US2003-632197/APPS  
SAVE TEMP L2 HOF197WPIAPP/A  
D IALL CMC

FILE 'STNGUIDE' ENTERED AT 10:12:38 ON 11 OCT 2005

FILE 'REGISTRY' ENTERED AT 10:13:30 ON 11 OCT 2005

L3 FILE 'HCAPLUS' ENTERED AT 10:13:33 ON 11 OCT 2005  
TRA L1 1- RN : 98 TERMS

L4 FILE 'REGISTRY' ENTERED AT 10:13:37 ON 11 OCT 2005  
98 SEA ABB=ON PLU=ON L3  
SAVE TEMP L4 HOF197REGAPP/A

FILE 'STNGUIDE' ENTERED AT 10:13:48 ON 11 OCT 2005

FILE 'REGISTRY' ENTERED AT 10:13:58 ON 11 OCT 2005  
D SCAN

FILE 'STNGUIDE' ENTERED AT 10:14:29 ON 11 OCT 2005

L5 FILE 'REGISTRY' ENTERED AT 10:29:04 ON 11 OCT 2005  
53 SEA ABB=ON PLU=ON L4 AND (C6 (S) NC5)/ESS  
L6 52 SEA ABB=ON PLU=ON L5 AND NRS>1  
L7 77 SEA ABB=ON PLU=ON L4 AND (C6 (S) C6)/ESS

FILE 'STNGUIDE' ENTERED AT 10:31:00 ON 11 OCT 2005

L8 FILE 'REGISTRY' ENTERED AT 10:34:31 ON 11 OCT 2005  
1 SEA ABB=ON PLU=ON QUINOLINE/CN  
D IDE RSD  
L9 1 SEA ABB=ON PLU=ON NAPHTHALENE/CN  
D IDE RSD

FILE 'STNGUIDE' ENTERED AT 10:36:18 ON 11 OCT 2005

L10 FILE 'REGISTRY' ENTERED AT 10:57:24 ON 11 OCT 2005  
0 SEA ABB=ON PLU=ON L4 AND C6-NC5/ES

FILE 'STNGUIDE' ENTERED AT 10:57:48 ON 11 OCT 2005

FILE 'REGISTRY' ENTERED AT 10:58:10 ON 11 OCT 2005  
L11        53 SEA ABB=ON PLU=ON NC5-C6/ES AND L4  
L12        9 SEA ABB=ON PLU=ON C6-C6/ES AND L4  
L13        52 SEA ABB=ON PLU=ON L11 AND NRS>1  
            D SCAN L12

FILE 'STNGUIDE' ENTERED AT 10:59:14 ON 11 OCT 2005

FILE 'REGISTRY' ENTERED AT 10:59:58 ON 11 OCT 2005  
L14        6 SEA ABB=ON PLU=ON L12 NOT L11  
L15        0 SEA ABB=ON PLU=ON L14 AND SI=0  
            D SCAN L14

FILE 'STNGUIDE' ENTERED AT 11:01:10 ON 11 OCT 2005

FILE 'REGISTRY' ENTERED AT 11:01:44 ON 11 OCT 2005  
L16        4 SEA ABB=ON PLU=ON L14 AND (SI/ELS OR BR/ELS)  
            D SCAN

FILE 'STNGUIDE' ENTERED AT 11:02:04 ON 11 OCT 2005

FILE 'REGISTRY' ENTERED AT 11:02:22 ON 11 OCT 2005  
L17        2 SEA ABB=ON PLU=ON L14 NOT L16  
            D SCAN  
L18        1 SEA ABB=ON PLU=ON L17 AND N/ELS  
            D SCAN  
            SAVE TEMP L18 HOF197RCLNAP/A  
L19        45 SEA ABB=ON PLU=ON L4 NOT (L13 OR L18)  
            D SCAN

FILE 'STNGUIDE' ENTERED AT 11:04:52 ON 11 OCT 2005

FILE 'REGISTRY' ENTERED AT 11:09:02 ON 11 OCT 2005  
L20        1 SEA ABB=ON PLU=ON L11 NOT L13  
            D SCAN  
            SAVE TEMP L13 HOF197RCLQUI/A

FILE 'STNGUIDE' ENTERED AT 11:10:23 ON 11 OCT 2005  
            D SAVED

FILE 'REGISTRY' ENTERED AT 11:11:13 ON 11 OCT 2005  
            D SCAN L13  
            D SCAN L18

FILE 'STNGUIDE' ENTERED AT 11:11:38 ON 11 OCT 2005

FILE HOME

FILE ZCAPLUS

Copyright of the articles to which records in this database refer is held by the publishers listed in the PUBLISHER (PB) field (available for records published or updated in Chemical Abstracts after December 26, 1996), unless otherwise indicated in the original publications. The CA Lexicon is the copyrighted intellectual property of the American Chemical Society and is provided to assist you in searching databases on STN. Any dissemination, distribution, copying, or storing of this information, without the prior written consent of CAS is

strictly prohibited.

FILE COVERS 1907 - 11 Oct 2005 VOL 143 ISS 16  
FILE LAST UPDATED: 10 Oct 2005 (20051010/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE HCAPLUS

Copyright of the articles to which records in this database refer is held by the publishers listed in the PUBLISHER (PB) field (available for records published or updated in Chemical Abstracts after December 26, 1996), unless otherwise indicated in the original publications. The CA Lexicon is the copyrighted intellectual property of the American Chemical Society and is provided to assist you in searching databases on STN. Any dissemination, distribution, copying, or storing of this information, without the prior written consent of CAS, is strictly prohibited.

FILE COVERS 1907 - 11 Oct 2005 VOL 143 ISS 16  
FILE LAST UPDATED: 10 Oct 2005 (20051010/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE STNGUIDE

FILE CONTAINS CURRENT INFORMATION.  
LAST RELOADED: Oct 7, 2005 (20051007/UP).

FILE WPIX

FILE LAST UPDATED: 6 OCT 2005 <20051006/UP>  
MOST RECENT DERWENT UPDATE: 200564 <200564/DW>  
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

>>> FOR A COPY OF THE DERWENT WORLD PATENTS INDEX STN USER GUIDE,  
PLEASE VISIT:  
[<<<](http://www.stn-international.de/training_center/patents/stn_guide.pdf)

>>> FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES, SEE  
<http://thomsonderwent.com/coverage/latestupdates/> <<<

>>> FOR INFORMATION ON ALL DERWENT WORLD PATENTS INDEX USER  
GUIDES, PLEASE VISIT:  
<http://thomsonderwent.com/support/userguides/> <<<

>>> NEW! FAST-ALERTING ACCESS TO NEWLY-PUBLISHED PATENT  
DOCUMENTATION NOW AVAILABLE IN DERWENT WORLD PATENTS INDEX  
FIRST VIEW - FILE WPIFV.  
FOR FURTHER DETAILS: <http://www.thomsonderwent.com/dwpifv> <<<

>>> THE CPI AND EPI MANUAL CODES HAVE BEEN REVISED FROM UPDATE 200501.  
PLEASE CHECK:  
<http://thomsonderwent.com/support/dwpiref/reftools/classification/code-rev>  
FOR DETAILS. <<<

**FILE REGISTRY**

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

**STRUCTURE FILE UPDATES:** 10 OCT 2005 HIGHEST RN 864908-12-3  
**DICTIONARY FILE UPDATES:** 10 OCT 2005 HIGHEST RN 864908-12-3

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH JULY 14, 2005

Please note that search-term pricing does apply when conducting SmartSELECT searches.

```
*****
*
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added,      *
* effective March 20, 2005. A new display format, IDERL, is now        *
* available and contains the CA role and document type information.   *
*****
```

Structure search iteration limits have been increased. See HELP SLIMITS for details.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

<http://www.cas.org/ONLINE/UG/regprops.html>

=> => log y

STN INTERNATIONAL LOGOFF AT 11:29:21 ON 11 OCT 2005

```
=> d que stat 159
L57          STR
           @11      17
C~~N          C~~N~~C      Cb @22    Cb @23    Hy @24    Hy @25    A @28
10    <      18    { @21      O          O
                   }          O
                   19
           12      16
           O          O
           |||      ||
           8 N~~C      15 N~~C~~C      Cb @31    Hy @32      33
           { @9      { @20      O
           O          O
           29      30
                           |||      ||
                           3      4      5
                           G2---C---G1
                           |     |
                           2     3     G3~G4
                           |     |
                           4     5     26   27
```

VAR G1=22/23/24/25  
 VAR G2=9/11/20/21  
 REP G3=(2-20) 28  
 VAR G4=31/32

## NODE ATTRIBUTES:

NSPEC IS RC AT 3  
 NSPEC IS RC AT 4  
 NSPEC IS RC AT 20  
 NSPEC IS RC AT 21  
 NSPEC IS RC AT 28  
 NSPEC IS RC AT 33  
 CONNECT IS E2 RC AT 8  
 CONNECT IS E1 RC AT 13  
 CONNECT IS E2 RC AT 15  
 CONNECT IS E1 RC AT 19  
 CONNECT IS M2 RC AT 22  
 CONNECT IS M2 RC AT 23  
 CONNECT IS M2 RC AT 24  
 CONNECT IS M2 RC AT 25  
 DEFAULT MLEVEL IS ATOM  
 GGCAT IS MCY UNS AT 22  
 GGCAT IS PCY UNS AT 23  
 GGCAT IS MCY UNS AT 24  
 GGCAT IS MCY UNS AT 25  
 DEFAULT ECLEVEL IS LIMITED  
 ECOUNT IS E6 C AT 22  
 ECOUNT IS E10 C AT 23  
 ECOUNT IS E5 C E1 N AT 24  
 ECOUNT IS E4 C E2 N AT 25  
 ECOUNT IS M3-X13 C AT 31  
 ECOUNT IS M1-X13 C AT 32

## GRAPH ATTRIBUTES:

RING(S) ARE ISOLATED OR EMBEDDED  
 NUMBER OF NODES IS 30

STEREO ATTRIBUTES: NONE  
 L59 57 SEA FILE=REGISTRY SSS FUL L57

100.0% PROCESSED 65451 ITERATIONS  
 SEARCH TIME: 00.00.01

57 ANSWERS

=> d que nos 163  
 L57 STR  
 L62 2 SEA FILE=BEILSTEIN SSS FUL L57  
 L63 1 SEA FILE=BEILSTEIN ABB=ON PLU=ON L62 NOT RN/FA

=> d his 166

(FILE 'HCAPLUS, USPATFULL, USPAT2, TOXCENTER, BEILSTEIN, CHEMCATS'  
 ENTERED AT 16:23:16 ON 11 OCT 2005)  
 L66 26 DUP REM L65 (8 DUPLICATES REMOVED)  
 SAVE TEMP L66 HOF197MULS1/A

FILE 'STNGUIDE' ENTERED AT 16:24:51 ON 11 OCT 2005

FILE 'STNGUIDE' ENTERED AT 16:25:23 ON 11 OCT 2005

FILE 'LREGISTRY' ENTERED AT 16:25:43 ON 11 OCT 2005

FILE 'REGISTRY' ENTERED AT 16:25:45 ON 11 OCT 2005

FILE 'ZCAPLUS' ENTERED AT 16:25:48 ON 11 OCT 2005  
FILE 'HCAPLUS' ENTERED AT 16:25:51 ON 11 OCT 2005  
FILE 'USPATFULL' ENTERED AT 16:25:58 ON 11 OCT 2005  
FILE 'USPAT2' ENTERED AT 16:26:02 ON 11 OCT 2005  
FILE 'TOXCENTER' ENTERED AT 16:26:06 ON 11 OCT 2005  
FILE 'BEILSTEIN' ENTERED AT 16:26:11 ON 11 OCT 2005  
FILE 'CHEMCATS' ENTERED AT 16:26:16 ON 11 OCT 2005  
FILE 'STNGUIDE' ENTERED AT 16:26:18 ON 11 OCT 2005  
FILE 'HCAPLUS, USPATFULL, BEILSTEIN, CHEMCATS' ENTERED AT 16:27:46 ON 11 OCT 2005  
FILE 'STNGUIDE' ENTERED AT 16:27:56 ON 11 OCT 2005  
FILE 'HCAPLUS, USPATFULL, BEILSTEIN, CHEMCATS' ENTERED AT 16:28:54 ON 11 OCT 2005  
FILE 'STNGUIDE' ENTERED AT 16:29:02 ON 11 OCT 2005  
FILE 'HCAPLUS, USPATFULL, BEILSTEIN, CHEMCATS' ENTERED AT 16:29:44 ON 11 OCT 2005  
FILE 'STNGUIDE' ENTERED AT 16:29:50 ON 11 OCT 2005  
FILE 'HCAPLUS, USPATFULL, BEILSTEIN, CHEMCATS' ENTERED AT 16:30:06 ON 11 OCT 2005  
FILE 'STNGUIDE' ENTERED AT 16:30:08 ON 11 OCT 2005  
FILE 'HCAPLUS, USPATFULL, BEILSTEIN, CHEMCATS' ENTERED AT 16:30:18 ON 11 OCT 2005  
FILE 'STNGUIDE' ENTERED AT 16:30:20 ON 11 OCT 2005  
FILE 'CHEMCATS' ENTERED AT 16:30:31 ON 11 OCT 2005  
FILE 'STNGUIDE' ENTERED AT 16:31:09 ON 11 OCT 2005  
FILE 'HCAPLUS, USPATFULL, BEILSTEIN, CHEMCATS' ENTERED AT 16:31:25 ON 11 OCT 2005  
FILE 'STNGUIDE' ENTERED AT 16:31:29 ON 11 OCT 2005  
FILE 'BEILSTEIN' ENTERED AT 16:32:00 ON 11 OCT 2005  
FILE 'STNGUIDE' ENTERED AT 16:32:01 ON 11 OCT 2005  
FILE 'BEILSTEIN' ENTERED AT 16:32:11 ON 11 OCT 2005  
FILE 'STNGUIDE' ENTERED AT 16:32:13 ON 11 OCT 2005  
FILE 'STNGUIDE' ENTERED AT 16:33:02 ON 11 OCT 2005

```
=> d que nos 166
L57          STR
L59          57 SEA FILE=REGISTRY SSS FUL L57
L65          34 SEA L59
L66          26 DUP REM L65 (8 DUPLICATES REMOVED)
```

```
=> d 164
L64          ANALYZE L59 1- LC `:      7 TERMS
```

TERM #	# OCC	# DOC	% DOC	LC
1	56	56	98.25	CA
2	56	56	98.25	CAPLUS
3	52	52	91.23	USPATFULL
4	46	46	80.70	TOXCENTER
5	1	1	1.75	BEILSTEIN
6	1	1	1.75	CHEMCATS
7	1	1	1.75	USPAT2

\*\*\*\*\* END OF L64\*\*\*

=>/d his ful

(FILE 'HOME' ENTERED AT 14:05:26 ON 11 OCT 2005)

FILE 'HCAPLUS' ENTERED AT 14:05:40 ON 11 OCT 2005  
ACT HOF197HCAAPP/A

L1 1 SEA ABB=ON PLU=ON US2003-632197/APPS

FILE 'STNGUIDE' ENTERED AT 14:05:56 ON 11 OCT 2005

FILE 'WPIX' ENTERED AT 14:06:04 ON 11 OCT 2005  
ACT HOF197WPIAPP/A

L2 1 SEA ABB=ON PLU=ON US2003-632197/APPS

FILE 'REGISTRY' ENTERED AT 14:06:24 ON 11 OCT 2005  
ACT HOF197RCLNAP/A

L3 ( 1) SEA ABB=ON PLU=ON US2003-632197/APPS  
L4 SEL PLU=ON L3 1- RN : 98 TERMS  
L5 ( 98) SEA ABB=ON PLU=ON L4  
L6 ( 53) SEA ABB=ON PLU=ON NC5-C6/ES AND L5  
L7 ( 9) SEA ABB=ON PLU=ON C6-C6/ES AND L5  
L8 ( 6) SEA ABB=ON PLU=ON L7 NOT L6  
L9 ( 4) SEA ABB=ON PLU=ON L8 AND (SI/ELS OR BR/ELS)  
L10 ( 2) SEA ABB=ON PLU=ON L8 NOT L9  
L11 1 SEA ABB=ON PLU=ON L10 AND N/ELS

-----  
ACT HOF197RCLQUI/A

L12 ( 1) SEA ABB=ON PLU=ON US2003-632197/APPS  
L13 SEL PLU=ON L12 1- RN : 98 TERMS  
L14 ( 98) SEA ABB=ON PLU=ON L13  
L15 ( 53) SEA ABB=ON PLU=ON NC5-C6/ES AND L14

L16           52 SEA ABB=ON PLU=ON L15 AND NRS>1  
-----  
L17           46 SEA ABB=ON PLU=ON L16 AND N>1  
L18           6 SEA ABB=ON PLU=ON L16 NOT L17  
              D SCAN

FILE 'STNGUIDE' ENTERED AT 14:07:38 ON 11 OCT 2005

FILE 'REGISTRY' ENTERED AT 14:08:14 ON 11 OCT 2005  
SAVE TEMP L17 HOF197RCLQ2/A

FILE 'STNGUIDE' ENTERED AT 14:08:27 ON 11 OCT 2005

FILE 'HCAPLUS' ENTERED AT 14:08:40 ON 11 OCT 2005

L19           3 SEA ABB=ON PLU=ON L16  
L20           1 SEA ABB=ON PLU=ON L17

FILE 'STNGUIDE' ENTERED AT 14:08:52 ON 11 OCT 2005  
D SAVED

FILE 'LREGISTRY' ENTERED AT 14:09:24 ON 11 OCT 2005

L21           STR

FILE 'REGISTRY' ENTERED AT 14:22:27 ON 11 OCT 2005

L22           5 SEA SSS SAM L21  
              D SCAN

FILE 'STNGUIDE' ENTERED AT 14:23:06 ON 11 OCT 2005

FILE 'LREGISTRY' ENTERED AT 14:24:52 ON 11 OCT 2005

L23           STR L21

FILE 'REGISTRY' ENTERED AT 14:35:54 ON 11 OCT 2005

L24           0 SEA SSS SAM L23

L25           1416999 SEA ABB=ON PLU=ON (C6 (S) NC5)/ESS

L26           1085117 SEA ABB=ON PLU=ON L25 AND N>1

L27           8 SEA SUB=L26 SSS SAM L23  
              D SCAN

FILE 'STNGUIDE' ENTERED AT 14:37:43 ON 11 OCT 2005

FILE 'REGISTRY' ENTERED AT 14:40:05 ON 11 OCT 2005

L28           355 SEA SUB=L26 SSS FUL L23  
              SAVE TEMP L28 HOF197PSET1/A

L29           46 SEA ABB=ON PLU=ON L28 AND L17

FILE 'STNGUIDE' ENTERED AT 14:41:06 ON 11 OCT 2005  
D SAVED

FILE 'HCAPLUS' ENTERED AT 14:41:40 ON 11 OCT 2005

L30           75 SEA ABB=ON PLU=ON L28  
L31           54 SEA ABB=ON PLU=ON L30 AND (AY<2002 OR PY<2002 OR PRY<2002)

FILE 'STNGUIDE' ENTERED AT 14:42:43 ON 11 OCT 2005

FILE 'REGISTRY' ENTERED AT 14:43:17 ON 11 OCT 2005

FILE 'LREGISTRY' ENTERED AT 14:43:54 ON 11 OCT 2005

L32           STR L23

FILE 'REGISTRY' ENTERED AT 14:45:53 ON 11 OCT 2005  
L33 10 SEA SUB=L28 SSS SAM L32  
D SCAN

FILE 'STNGUIDE' ENTERED AT 14:46:59 ON 11 OCT 2005

FILE 'LREGISTRY' ENTERED AT 14:48:19 ON 11 OCT 2005  
L34 STR L32

FILE 'REGISTRY' ENTERED AT 14:49:19 ON 11 OCT 2005  
L35 6 SEA SUB=L28 SSS SAM L34  
D SCAN

FILE 'STNGUIDE' ENTERED AT 14:49:39 ON 11 OCT 2005

FILE 'LREGISTRY' ENTERED AT 14:50:34 ON 11 OCT 2005  
L36 STR L34

FILE 'REGISTRY' ENTERED AT 14:53:22 ON 11 OCT 2005  
L37 0 SEA SUB=L28 SSS SAM L36  
D QUE STAT

FILE 'STNGUIDE' ENTERED AT 14:53:41 ON 11 OCT 2005

FILE 'LREGISTRY' ENTERED AT 14:54:28 ON 11 OCT 2005  
L38 STR L36

FILE 'REGISTRY' ENTERED AT 14:55:03 ON 11 OCT 2005  
L39 0 SEA SUB=L28 SSS SAM L38  
D QUE STAT

FILE 'STNGUIDE' ENTERED AT 14:55:18 ON 11 OCT 2005

FILE 'REGISTRY' ENTERED AT 14:56:05 ON 11 OCT 2005  
L40 84 SEA SUB=L28 SSS FUL L38  
SAVE TEMP L40 HOF197RSET1/A

L41 46 SEA ABB=ON PLU=ON L40 AND L17

L42 38 SEA ABB=ON PLU=ON L40 NOT L17  
D SCAN

FILE 'STNGUIDE' ENTERED AT 14:58:08 ON 11 OCT 2005

FILE 'LREGISTRY' ENTERED AT 15:02:28 ON 11 OCT 2005  
L43 STR L38

FILE 'REGISTRY' ENTERED AT 15:03:28 ON 11 OCT 2005  
L44 0 SEA SUB=L40 SSS SAM L43

L45 71 SEA SUB=L40 SSS FUL L43  
SAVE TEMP L45 HOF197RSET2/ HOF197RSET2/A

L46 46 SEA ABB=ON PLU=ON L45 AND L17

L47 25 SEA ABB=ON PLU=ON L45 NOT L17  
D SCAN

FILE 'STNGUIDE' ENTERED AT 15:05:00 ON 11 OCT 2005

FILE 'HCAPLUS' ENTERED AT 15:07:09 ON 11 OCT 2005  
L48 3 SEA ABB=ON PLU=ON L47  
D IBIB 1-3

FILE 'STNGUIDE' ENTERED AT 15:07:27 ON 11 OCT 2005

D COST

FILE 'STNGUIDE' ENTERED AT 15:08:35 ON 11 OCT 2005  
D SAVED

L49 FILE 'LREGISTRY' ENTERED AT 15:10:39 ON 11 OCT 2005  
STR L43

FILE 'STNGUIDE' ENTERED AT 15:14:50 ON 11 OCT 2005

L50 FILE 'REGISTRY' ENTERED AT 15:14:57 ON 11 OCT 2005  
2 SEA SSS SAM L49  
D SCAN

L51 FILE 'LREGISTRY' ENTERED AT 15:16:55 ON 11 OCT 2005  
STR L49

L52 FILE 'REGISTRY' ENTERED AT 15:17:39 ON 11 OCT 2005  
4 SEA SSS SAM L51  
D SCAN

FILE 'STNGUIDE' ENTERED AT 15:17:54 ON 11 OCT 2005

L53 FILE 'LREGISTRY' ENTERED AT 15:21:38 ON 11 OCT 2005  
STR L51

L54 FILE 'REGISTRY' ENTERED AT 15:22:20 ON 11 OCT 2005  
0 SEA SSS SAM L53  
D QUE STAT

FILE 'STNGUIDE' ENTERED AT 15:22:53 ON 11 OCT 2005

L55 FILE 'LREGISTRY' ENTERED AT 15:23:52 ON 11 OCT 2005  
STR L53

L56 FILE 'REGISTRY' ENTERED AT 15:24:44 ON 11 OCT 2005  
0 SEA SSS SAM L55  
D QUE STAT

FILE 'STNGUIDE' ENTERED AT 15:24:54 ON 11 OCT 2005

L57 FILE 'LREGISTRY' ENTERED AT 15:29:55 ON 11 OCT 2005  
STR L55

L58 FILE 'REGISTRY' ENTERED AT 15:30:49 ON 11 OCT 2005  
0 SEA SSS SAM L57  
D QUE STAT

FILE 'STNGUIDE' ENTERED AT 15:31:00 ON 11 OCT 2005

L59 FILE 'REGISTRY' ENTERED AT 15:35:36 ON 11 OCT 2005  
57 SEA SSS FUL L57  
SAVE TEMP L59 HOF197PSET2/A  
L60 46 SEA ABB=ON PLU=ON L59 AND L17  
L61 11 SEA ABB=ON PLU=ON L59 NOT L17  
D SCAN

FILE 'STNGUIDE' ENTERED AT 15:37:08 ON 11 OCT 2005

FILE 'STNGUIDE' ENTERED AT 15:42:21 ON 11 OCT 2005

D SAVED  
D QUE STAT L59  
D QUE STAT L59

FILE 'REGISTRY' ENTERED AT 16:15:19 ON 11 OCT 2005  
D SCAN L47

FILE 'STNGUIDE' ENTERED AT 16:15:44 ON 11 OCT 2005  
D SAVED

FILE 'BEILSTEIN' ENTERED AT 16:19:14 ON 11 OCT 2005  
D QUE L59

L62 2 SEA SSS FUL L57  
L63 1 SEA ABB=ON PLU=ON L62 NOT RN/FA  
SAVE TEMP L63 HOF197BEI1/A

FILE 'MARPAT' ENTERED AT 16:21:21 ON 11 OCT 2005

FILE 'STNGUIDE' ENTERED AT 16:21:53 ON 11 OCT 2005

FILE 'REGISTRY' ENTERED AT 16:22:05 ON 11 OCT 2005  
L64 ANALYZE PLU=ON L59 1- LC : 7 TERMS  
D

FILE 'STNGUIDE' ENTERED AT 16:22:38 ON 11 OCT 2005

FILE 'HCAPLUS, USPATFULL, USPAT2, TOXCENTER, BEILSTEIN, CHEMCATS' ENTERED  
AT 16:23:16 ON 11 OCT 2005

L65 34 SEA ABB=ON PLU=ON L59  
L66 26 DUP REM L65 (8 DUPLICATES REMOVED)  
ANSWERS '1-10' FROM FILE HCAPLUS  
ANSWERS '11-22' FROM FILE USPATFULL  
ANSWER '23' FROM FILE BEILSTEIN  
ANSWERS '24-26' FROM FILE CHEMCATS  
SAVE TEMP L66 HOF197MULS1/A  
D SAVED

FILE 'STNGUIDE' ENTERED AT 16:24:51 ON 11 OCT 2005

FILE 'STNGUIDE' ENTERED AT 16:25:23 ON 11 OCT 2005

FILE 'LREGISTRY' ENTERED AT 16:25:43 ON 11 OCT 2005

FILE 'REGISTRY' ENTERED AT 16:25:45 ON 11 OCT 2005

FILE 'ZCAPLUS' ENTERED AT 16:25:48 ON 11 OCT 2005

FILE 'HCAPLUS' ENTERED AT 16:25:51 ON 11 OCT 2005

FILE 'USPATFULL' ENTERED AT 16:25:58 ON 11 OCT 2005

FILE 'USPAT2' ENTERED AT 16:26:02 ON 11 OCT 2005

FILE 'TOXCENTER' ENTERED AT 16:26:06 ON 11 OCT 2005

FILE 'BEILSTEIN' ENTERED AT 16:26:11 ON 11 OCT 2005

FILE 'CHEMCATS' ENTERED AT 16:26:16 ON 11 OCT 2005

FILE 'STNGUIDE' ENTERED AT 16:26:18 ON 11 OCT 2005

D QUE STAT L59  
D QUE NOS L66  
D L64

FILE 'HCAPLUS, USPATFULL, BEILSTEIN, CHEMCATS' ENTERED AT 16:27:46 ON 11 OCT 2005

FILE 'STNGUIDE' ENTERED AT 16:27:56 ON 11 OCT 2005

FILE 'HCAPLUS, USPATFULL, BEILSTEIN, CHEMCATS' ENTERED AT 16:28:54 ON 11 OCT 2005

D L66 IBIB ED AB IND HITSTR RETABLE 1-10

FILE 'STNGUIDE' ENTERED AT 16:29:02 ON 11 OCT 2005

FILE 'HCAPLUS, USPATFULL, BEILSTEIN, CHEMCATS' ENTERED AT 16:29:44 ON 11 OCT 2005

D IBIB AB HITSTR L66 11-22

FILE 'STNGUIDE' ENTERED AT 16:29:50 ON 11 OCT 2005

FILE 'HCAPLUS, USPATFULL, BEILSTEIN, CHEMCATS' ENTERED AT 16:30:06 ON 11 OCT 2005

D L66 IDE 23

FILE 'STNGUIDE' ENTERED AT 16:30:08 ON 11 OCT 2005

FILE 'HCAPLUS, USPATFULL, BEILSTEIN, CHEMCATS' ENTERED AT 16:30:18 ON 11 OCT 2005

D RX L66 23

FILE 'STNGUIDE' ENTERED AT 16:30:20 ON 11 OCT 2005

FILE 'CHEMCATS' ENTERED AT 16:30:31 ON 11 OCT 2005

FILE 'STNGUIDE' ENTERED AT 16:31:09 ON 11 OCT 2005

FILE 'HCAPLUS, USPATFULL, BEILSTEIN, CHEMCATS' ENTERED AT 16:31:25 ON 11 OCT 2005

D IALL L66 24-26

FILE 'STNGUIDE' ENTERED AT 16:31:29 ON 11 OCT 2005

D QUE NOS L63

FILE 'BEILSTEIN' ENTERED AT 16:32:00 ON 11 OCT 2005

D IDE L63

FILE 'STNGUIDE' ENTERED AT 16:32:01 ON 11 OCT 2005

FILE 'BEILSTEIN' ENTERED AT 16:32:11 ON 11 OCT 2005

D L63 RX

FILE 'STNGUIDE' ENTERED AT 16:32:13 ON 11 OCT 2005

FILE 'STNGUIDE' ENTERED AT 16:33:02 ON 11 OCT 2005

D QUE STAT L59

D QUE NOS L63

D QUE NOS L66

D L64

FILE HOME

FILE HCAPLUS

Copyright of the articles to which records in this database refer is held by the publishers listed in the PUBLISHER (PB) field (available for records published or updated in Chemical Abstracts after December 26, 1996), unless otherwise indicated in the original publications. The CA Lexicon is the copyrighted intellectual property of the American Chemical Society and is provided to assist you in searching databases on STN. Any dissemination, distribution, copying, or storing of this information, without the prior written consent of CAS, is strictly prohibited.

FILE COVERS 1907 - 11 Oct 2005 VOL 143 ISS 16  
FILE LAST UPDATED: 10 Oct 2005 (20051010/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE STNGUIDE  
FILE CONTAINS CURRENT INFORMATION.  
LAST RELOADED: Oct 7, 2005 (20051007/UP).

FILE WPIX  
FILE LAST UPDATED: 6 OCT 2005 <20051006/UP>  
MOST RECENT DERWENT UPDATE: 200564 <200564/DW>  
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

>>> FOR A COPY OF THE DERWENT WORLD PATENTS INDEX STN USER GUIDE,  
PLEASE VISIT:  
[<<<](http://www.stn-international.de/training_center/patents/stn_guide.pdf)

>>> FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES, SEE  
<http://thomsonderwent.com/coverage/latestupdates/> <<<

>>> FOR INFORMATION ON ALL DERWENT WORLD PATENTS INDEX USER  
GUIDES, PLEASE VISIT:  
<http://thomsonderwent.com/support/userguides/> <<<

>>> NEW! FAST-ALERTING ACCESS TO NEWLY-PUBLISHED PATENT  
DOCUMENTATION NOW AVAILABLE IN DERWENT WORLD PATENTS INDEX  
FIRST VIEW - FILE WPIFV.  
FOR FURTHER DETAILS: [<<<](http://www.thomsonderwent.com/dwpifv)

>>> THE CPI AND EPI MANUAL CODES HAVE BEEN REVISED FROM UPDATE 200501.  
PLEASE CHECK:  
<http://thomsonderwent.com/support/dwpieref/reftools/classification/code-rev>  
FOR DETAILS. <<<

FILE REGISTRY  
Property values tagged with IC are from the ZIC/VINITI data file  
provided by InfoChem.

STRUCTURE FILE UPDATES: 10 OCT 2005 HIGHEST RN 864908-12-3  
DICTIONARY FILE UPDATES: 10 OCT 2005 HIGHEST RN 864908-12-3

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH JULY 14, 2005

Please note that search-term pricing does apply when conducting SmartSELECT searches.

\*\*\*\*\*  
\*  
\* The CA roles and document type information have been removed from \*  
\* the IDE default display format and the ED field has been added, \*  
\* effective March 20, 2005. A new display format, IDERL, is now \*  
\* available and contains the CA role and document type information. \*  
\*  
\*\*\*\*\*

Structure search iteration limits have been increased. See HELP SLIMITS for details.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

<http://www.cas.org/ONLINE/UG/regprops.html>

FILE LREGISTRY  
LREGISTRY IS A STATIC LEARNING FILE

NEW CAS INFORMATION USE POLICIES, ENTER HELP USAGETERMS FOR DETAILS.

FILE BEILSTEIN  
FILE RELOADED ON OCTOBER 20, 2002  
FILE LAST UPDATED ON JUNE 29, 2005

FILE COVERS 1771 TO 2005.  
FILE CONTAINS 9,271,550 SUBSTANCES

>>>PLEASE NOTE: Reaction Data and substance data are stored in separate documents and can not be searched together in one query. Reaction data for BEILSTEIN compounds may be displayed immediately with the display codes PRE (preparations) and REA (reactions). A substance answer set retrieved after the search for a chemical name, a compounds with available reaction information by combining with PRE/FA, REA/FA or more generally with RX/FA. The BEILSTEIN Registry Number (BRN) is the link between a BEILSTEIN compound and belonging reactions. For more detailed reaction searches BRNs can be searched as reaction partner BRNs Reactant BRN (RX.RBRN) or Product BRN (RX.PBRN).<<<

>>> FOR SEARCHING PREPARATIONS SEE HELP PRE <<<

\*\*\*\*\*  
\* PLEASE NOTE THAT THERE ARE NO FORMATS FREE OF COST. \*  
\* SET NOTICE FEATURE: THE COST ESTIMATES CALCULATED FOR SET NOTICE \*  
\* ARE BASED ON THE HIGHEST PRICE CATEGORY. THEREFORE; THESE \*  
\* ESTIMATES MAY NOT REFLECT THE ACTUAL COSTS. \*  
\* FOR PRICE INFORMATION SEE HELP COST \*  
\*\*\*\*\*

NEW

- \* PATENT NUMBERS (PN) AND BABS ACCESSION NUMBERS (BABSAN) CAN NOW BE SEARCHED, SELECTED AND TRANSFERRED.
- \* NEW DISPLAY FORMATS ALLREF, ALLP AND BABSAN SHOW ALL REFERENCES, ALL PATENT REFERENCES, OR ALL BABS ACCESSION NUMBERS FOR A COMPOUND AT A GLANCE.

FILE MARPAT

FILE CONTENT: 1988-PRESENT (VOL 143 ISS 15) (20051007/ED)

MOST RECENT CITATIONS FOR PATENTS FROM FIVE MAJOR ISSUING AGENCIES  
(COVERAGE TO THESE DATES IS NOT COMPLETE):

US 6916824 12 JUL 2005  
DE 10359831 14 JUL 2005  
EP 1550665 06 JUL 2005  
JP 2005183717 07 JUL 2005  
WO 2005079855 01 SEP 2005

Expanded G-group definition display now available.

New CAS Information Use Policies, enter HELP USAGETERMS for details.

FILE USPATFULL

FILE COVERS 1971 TO PATENT PUBLICATION DATE: 6 Oct 2005 (20051006/PD)  
FILE LAST UPDATED: 6 Oct 2005 (20051006/ED)  
HIGHEST GRANTED PATENT NUMBER: US6952836  
HIGHEST APPLICATION PUBLICATION NUMBER: US2005223461  
CA INDEXING IS CURRENT THROUGH 6 Oct 2005 (20051006/UPCA)  
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 6 Oct 2005 (20051006/PD)  
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Aug 2005  
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Aug 2005

```
>>> USPAT2 is now available. USPATFULL contains full text of the <<<
>>> original, i.e., the earliest published granted patents or <<<
>>> applications. USPAT2 contains full text of the latest US <<<
>>> publications, starting in 2001, for the inventions covered in <<<
>>> USPATFULL. A USPATFULL record contains not only the original <<<
>>> published document but also a list of any subsequent <<<
>>> publications. The publication number, patent kind code, and <<<
>>> publication date for all the US publications for an invention <<<
>>> are displayed in the PI (Patent Information) field of USPATFULL <<<
>>> records and may be searched in standard search fields, e.g., /PN, <<<
>>> /PK, etc. <<<

>>> USPATFULL and USPAT2 can be accessed and searched together <<<
>>> through the new cluster USPATALL. Type FILE USPATALL to <<<
>>> enter this cluster. <<<
>>>
>>> Use USPATALL when searching terms such as patent assignees, <<<
>>> classifications, or claims, that may potentially change from <<<
>>> the earliest to the latest publication. <<<
```

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE USPAT2

FILE COVERS 2001 TO PUBLICATION DATE: 11 Oct 2005 (20051011/PD)  
FILE LAST UPDATED: 11 Oct 2005 (20051011/ED)  
HIGHEST GRANTED PATENT NUMBER: US2005054189

HIGHEST APPLICATION PUBLICATION NUMBER: US2005222704  
CA INDEXING IS CURRENT THROUGH 11 Oct 2005 (20051011/UPCA)  
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 11 Oct 2005 (20051011/PD)  
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Aug 2005  
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Aug 2005

USPAT2 is a companion file to USPATFULL. USPAT2 contains full text of the latest US publications, starting in 2001, for the inventions covered in USPATFULL. USPATFULL contains full text of the original published US patents from 1971 to date and the original applications from 2001. In addition, a USPATFULL record for an invention contains a complete list of publications that may be searched in standard search fields, e.g., /PN, /PK, etc.

USPATFULL and USPAT2 can be accessed and searched together through the new cluster USPATALL. Type FILE USPATALL to enter this cluster.

Use USPATALL when searching terms such as patent assignees, classifications, or claims, that may potentially change from the earliest to the latest publication.

#### FILE TOXCENTER

FILE COVERS 1907 TO 11 Oct 2005 (20051011/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TOXCENTER has been enhanced with new files segments and search fields. See HELP CONTENT for more information.

TOXCENTER thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2005 vocabulary. See <http://www.nlm.nih.gov/mesh/> and [http://www.nlm.nih.gov/pubs/techbull/nd04/nd04\\_mesh.html](http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html) for a description of changes.

#### FILE CHEMCATS

FILE LAST UPDATED 08 OCTOBER 2005 (20051008/UP)

For details on recent updates in CHEMCATS, enter NEWS FILE at an arrow prompt. For the list of suppliers currently in the file, enter HELP SPA, HELP SPBC, HELP SPDH, HELP SPIN, HELP SPOP, and HELP SPQZ. For the list of current catalogs, enter HELP CTA, HELP CTBC, HELP CTDH, HELP CTIN, HELP CTOP, and HELP CTQZ.

This database is provided on an "as is" basis. Please consult the suppliers for current information regarding pricing, regional availability, available quantities, purities, etc. THERE ARE NO WARRANTIES OF ANY KIND, EITHER EXPRESSED OR IMPLIED. ACS is not liable for any loss of profit, goodwill or any other damages arising out of the use of this database.

CHEMCATS now contains more than 8 million records. See HELP CONTENT and NEWS FILE for details.

#### FILE ZCAPLUS

Copyright of the articles to which records in this database refer is held by the publishers listed in the PUBLISHER (PB) field (available for records published or updated in Chemical Abstracts after December 26, 1996), unless otherwise indicated in the original publications. The CA Lexicon is the copyrighted intellectual property of the American Chemical Society and is provided to assist you in searching databases on STN. Any dissemination, distribution, copying, or storing of this information, without the prior written consent of CAS is strictly prohibited.

FILE COVERS 1907 - 11 Oct 2005 VOL 143 ISS 16  
FILE LAST UPDATED: 10 Oct 2005 (20051010/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> => d his 111

(FILE 'HCAPLUS, TOXCENTER, USPATFULL' ENTERED AT 14:44:48 ON 12 OCT 2005)  
L11 2 DUP REM L10 (1 DUPLICATE REMOVED)

=> d que 111  
L1 ( 1) SEA FILE=HCAPLUS ABB=ON PLU=ON US2003-632197/APPS  
L2 SEL PLU=ON L1 1- RN : 98 TERMS  
L3 ( 98) SEA FILE=REGISTRY ABB=ON PLU=ON L2  
L4 ( 53) SEA FILE=REGISTRY ABB=ON PLU=ON NC5-C6/ES AND L3  
L5 ( 9) SEA FILE=REGISTRY ABB=ON PLU=ON C6-C6/ES AND L3  
L6 ( 6) SEA FILE=REGISTRY ABB=ON PLU=ON L5 NOT L4  
L7 ( 4) SEA FILE=REGISTRY ABB=ON PLU=ON L6 AND (SI/ELS OR BR/ELS)  
L8 ( 2) SEA FILE=REGISTRY ABB=ON PLU=ON L6 NOT L7  
L9 1 SEA FILE=REGISTRY ABB=ON PLU=ON L8 AND N/ELS  
L10 3 SEA L9  
L11 2 DUP REM L10 (1 DUPLICATE REMOVED)

=> d his ful

(FILE 'HOME' ENTERED AT 14:42:08 ON 12 OCT 2005)

FILE 'REGISTRY' ENTERED AT 14:42:17 ON 12 OCT 2005  
ACT HOF197RCLNAP/A

-----  
L1 ( 1) SEA ABB=ON PLU=ON US2003-632197/APPS  
L2 SEL PLU=ON L1 1- RN : 98 TERMS  
L3 ( 98) SEA ABB=ON PLU=ON L2  
L4 ( 53) SEA ABB=ON PLU=ON NC5-C6/ES AND L3  
L5 ( 9) SEA ABB=ON PLU=ON C6-C6/ES AND L3  
L6 ( 6) SEA ABB=ON PLU=ON L5 NOT L4  
L7 ( 4) SEA ABB=ON PLU=ON L6 AND (SI/ELS OR BR/ELS)  
L8 ( 2) SEA ABB=ON PLU=ON L6 NOT L7  
L9 1 SEA ABB=ON PLU=ON L8 AND N/ELS  
-----  
D SCAN

FILE 'STNGUIDE' ENTERED AT 14:43:11 ON 12 OCT 2005

FILE 'HCAPLUS' ENTERED AT 14:43:44 ON 12 OCT 2005

FILE 'ZCAPLUS' ENTERED AT 14:43:47 ON 12 OCT 2005  
 FILE 'LREGISTRY' ENTERED AT 14:43:50 ON 12 OCT 2005  
 FILE 'REGISTRY' ENTERED AT 14:43:52 ON 12 OCT 2005  
 FILE 'STNGUIDE' ENTERED AT 14:43:54 ON 12 OCT 2005  
 D QUE L9

FILE 'REGISTRY' ENTERED AT 14:44:08 ON 12 OCT 2005  
 D IDE L9

FILE 'STNGUIDE' ENTERED AT 14:44:09 ON 12 OCT 2005

FILE 'HCAPLUS, TOXCENTER, USPATFULL' ENTERED AT 14:44:48 ON 12 OCT 2005

L10           3 SEA ABB=ON PLU=ON L9  
 L11           2 DUP REM L10 (1 DUPLICATE REMOVED)  
               ANSWER '1' FROM FILE HCAPLUS  
               ANSWER '2' FROM FILE USPATFULL  
               SAVE TEMP L11 HOF197MULS2/A  
               D SAVED

FILE 'STNGUIDE' ENTERED AT 14:45:55 ON 12 OCT 2005  
 D QUE L11

FILE 'HCAPLUS, USPATFULL' ENTERED AT 14:46:26 ON 12 OCT 2005  
 D IBIB ED AB HITSTR L11 1

FILE 'STNGUIDE' ENTERED AT 14:46:27 ON 12 OCT 2005

FILE 'HCAPLUS, USPATFULL' ENTERED AT 14:46:53 ON 12 OCT 2005  
 D IBIB AB HITSTR L11 2

FILE 'STNGUIDE' ENTERED AT 14:46:53 ON 12 OCT 2005

FILE 'WPIX' ENTERED AT 14:47:36 ON 12 OCT 2005  
 ACT HOF197WPIAPP/A

-----  
 L12           1 SEA ABB=ON PLU=ON US2003-632197/APPS  
 -----  
 L13           SELECT L12 1- DCN  
               1 SEA ABB=ON PLU=ON (RADLBS/DCN OR RADLCX/DCN OR RADLCZ/DCN OR  
               RADLD1/DCN OR RADLD3/DCN OR RADLD6/DCN OR RADL2W/DCN OR  
               RADL2X/DCN OR RADL2Y/DCN OR RADL2Z/DCN OR RADL3C/DCN OR  
               RADL3E/DCN OR RADL3J/DCN OR RADL3K/DCN OR RADL3W/DCN OR  
               RADL3Y/DCN OR RADL3Z/DCN OR RADL30/DCN OR RADL4D/DCN OR  
               RADL4J/DCN OR RADL40/DCN OR RADL41/DCN OR RADL42/DCN OR  
               RADL47/DCN OR RADL81/DCN OR RADL89/DCN OR 0125-21301/DCN OR  
               0125-21302/DCN OR 0125-21303/DCN OR 0125-21304/DCN OR 0125-2130  
               5/DCN OR 0125-21306/DCN OR 0125-21307/DCN OR 0125-21308/DCN OR  
               0125-21309/DCN OR 0125-21310/DCN OR 0125-21311/DCN OR 0125-2131  
               2/DCN OR 0125-21313/DCN OR 0125-21314/DCN)

FILE 'STNGUIDE' ENTERED AT 14:48:23 ON 12 OCT 2005

FILE 'WPIX' ENTERED AT 15:00:23 ON 12 OCT 2005  
 D CMC L12

FILE 'STNGUIDE' ENTERED AT 15:00:26 ON 12 OCT 2005

L14 FILE 'WPIX' ENTERED AT 15:04:55 ON 12 OCT 2005  
 27282 SEA ABB=ON PLU=ON ((D621 OR D622)(P) (G011 OR G012 OR G013  
 OR G014 OR G015 OR G016 OR G221 OR F431 OR F541))/M0,M1,M2,M3,M  
 4,M5,M6

FILE 'STNGUIDE' ENTERED AT 15:05:31 ON 12 OCT 2005

L15 FILE 'HCAPLUS' ENTERED AT 15:05:58 ON 12 OCT 2005  
 32505 SEA ABB=ON PLU=ON ?HYDANTOI? OR ?HYDROXAM?  
 L16 QUE ABB=ON PLU=ON ?HYDANTOI? OR ?HYDROXAM?

FILE 'STNGUIDE' ENTERED AT 15:06:12 ON 12 OCT 2005

L17 FILE 'WPIX' ENTERED AT 15:06:19 ON 12 OCT 2005  
 253 SEA ABB=ON PLU=ON (L13 OR L14) AND (?HYDANTOI?/BIX OR  
 ?HYDROXAM?/BIX)

FILE 'STNGUIDE' ENTERED AT 15:07:06 ON 12 OCT 2005

L18 FILE 'HCAPLUS' ENTERED AT 15:10:17 ON 12 OCT 2005  
 QUE ABB=ON PLU=ON MMP OR (?MATRIX?(2A) (?METALLOPROT? OR  
 (?METALLO(1W) PROT?))) OR TNF OR ((?TUMOR? OR ?TUMOUR?)(2A) ?NECR  
 O?) OR TACE OR (?ALPHA?(2A) (?CONVERT? OR ?CONVERS?))

L19 FILE 'WPIX' ENTERED AT 15:10:39 ON 12 OCT 2005  
 48 SEA ABB=ON PLU=ON L17 AND (MMP/BIX OR (?MATRIX?/BIX(2A) (?META  
 LLOPROT?/BIX OR (?METALLO/BIX(1W) PROT?/BIX))) OR TNF/BIX OR  
 ((?TUMOR?/BIX OR ?TUMOUR?/BIX)(2A) ?NECRO?/BIX) OR TACE/BIX OR  
 (?ALPHA?/BIX(2A) (?CONVERT?/BIX OR ?CONVERS?/BIX)))

L20 168 SEA ABB=ON PLU=ON (?HYDANTOI?/BIX OR ?HYDROXAM?/BIX) (7A)  
 (MMP/BIX OR (?MATRIX?/BIX(2A) (?METALLOPROT?/BIX OR (?METALLO/BI  
 X(1W) PROT?/BIX))) OR TNF/BIX OR ((?TUMOR?/BIX OR ?TUMOUR?/BIX)(  
 2A) ?NECRO?/BIX) OR TACE/BIX OR (?ALPHA?/BIX(2A) (?CONVERT?/BIX  
 OR ?CONVERS?/BIX)))

L21 19 SEA ABB=ON PLU=ON L19 AND L20

L22 0 SEA ABB=ON PLU=ON L12 AND L21

L23 328 SEA ABB=ON PLU=ON (?HYDANTOI?/BIX OR ?HYDROXAM?/BIX) (L)  
 (MMP/BIX OR (?MATRIX?/BIX(2A) (?METALLOPROT?/BIX OR (?METALLO/BI  
 X(1W) PROT?/BIX))) OR TNF/BIX OR ((?TUMOR?/BIX OR ?TUMOUR?/BIX)(  
 2A) ?NECRO?/BIX) OR TACE/BIX OR (?ALPHA?/BIX(2A) (?CONVERT?/BIX  
 OR ?CONVERS?/BIX)))

L24 1 SEA ABB=ON PLU=ON L23 AND L12

L25 40 SEA ABB=ON PLU=ON (L13 OR L14) AND L23

FILE 'STNGUIDE' ENTERED AT 15:15:33 ON 12 OCT 2005

L26 FILE 'HCAPLUS' ENTERED AT 15:18:49 ON 12 OCT 2005  
 QUE ABB=ON PLU=ON ?INHIBIT? OR ?REPRESS? OR ?SUPRESS? OR  
 ?DISRUPT? OR ?INTERRUPT? OR ?ANTAGON? OR ?PROHIBIT? OR  
 ?PREVENT? OR ?IMPED? OR ?REDUC? OR ?DEPRESS? OR ?BLOCK? OR  
 STOP? OR ?RETARD? OR SLOW?

L27 FILE 'WPIX' ENTERED AT 15:19:03 ON 12 OCT 2005  
 3929 SEA ABB=ON PLU=ON (MMP/BIX OR (?MATRIX?/BIX(2A) (?METALLOPROT?  
 /BIX OR (?METALLO/BIX(1W) PROT?/BIX))) OR TNF/BIX OR ((?TUMOR?/B  
 IX OR ?TUMOUR?/BIX)(2A) ?NECRO?/BIX) OR TACE/BIX OR (?ALPHA?/BIX  
 (2A) (?CONVERT?/BIX OR ?CONVERS?/BIX))) (7A) (?INHIBIT?/BIX OR  
 ?REPRESS?/BIX OR ?SUPRESS?/BIX OR ?DISRUPT?/BIX OR ?INTERRUPT?/  
 BIX OR ?ANTAGON?/BIX OR ?PROHIBIT?/BIX OR ?PREVENT?/BIX OR  
 ?IMPED?/BIX OR ?REDUC?/BIX OR ?DEPRESS?/BIX OR ?BLOCK?/BIX OR

L28 STOP?/BIX OR ?RETARD?/BIX OR SLOW?/BIX)  
 304 SEA ABB=ON PLU=ON L27 (L) (?HYDANTOI?/BIX OR ?HYDROXAM?/BIX)

L29 38 SEA ABB=ON PLU=ON L25 AND L28  
 D TRI 1-3

L30 33 SEA ABB=ON PLU=ON L29 AND (AY<2003 OR PY<2003 OR PRY<2003)  
 SAVE TEMP L29 HOF197WPIP/A

FILE 'MEDLINE' ENTERED AT 15:58:41 ON 12 OCT 2005

L31 20358 SEA ABB=ON PLU=ON L18 (5A) L26

L32 501 SEA ABB=ON PLU=ON L16 (10A) L16  
 E HYDANTOINS/CT  
 E E43+ALL

L33 15228 SEA ABB=ON PLU=ON HYDANTOINS+PFT,NT/CT

L34 485 SEA ABB=ON PLU=ON L33 (L) AA

L35 38 SEA ABB=ON PLU=ON L32 AND L34  
 D TRI 1-3

FILE 'STNGUIDE' ENTERED AT 16:00:41 ON 12 OCT 2005

FILE 'HCAPLUS' ENTERED AT 16:02:19 ON 12 OCT 2005

L36 QUE ABB=ON PLU=ON ?QUINOLIN?

L37 QUE ABB=ON PLU=ON ?PHENYL? OR ?BENZYL? OR ?NAPHTHYL? OR  
 ?NAPHTHENYL? OR ?PYRIDYL? OR ?PYRIDIN? OR ?PYRIMIDYL? OR  
 ?PYRIMIDIN? OR ?BENZENE?

FILE 'STNGUIDE' ENTERED AT 16:02:37 ON 12 OCT 2005

FILE 'MEDLINE' ENTERED AT 16:02:40 ON 12 OCT 2005

L38 4627 SEA ABB=ON PLU=ON L16 (L) (L36 OR L37)

L39 38 SEA ABB=ON PLU=ON L35 AND L38  
 SAVE TEMP L39 HOF197MEDP/A

FILE 'STNGUIDE' ENTERED AT 16:03:31 ON 12 OCT 2005

D SAVED  
 D QUE L11

FILE HOME

#### FILE REGISTRY

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 11 OCT 2005 HIGHEST RN 865062-68-6  
 DICTIONARY FILE UPDATES: 11 OCT 2005 HIGHEST RN 865062-68-6

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH JULY 14, 2005

Please note that search-term pricing does apply when conducting SmartSELECT searches.

\*\*\*\*\*

\* The CA roles and document type information have been removed from \*  
 \* the IDE default display format and the ED field has been added, \*  
 \* effective March 20, 2005. A new display format, IDERL, is now \*  
 \* available and contains the CA role and document type information. \*

\*\*\*\*\*  
Structure search iteration limits have been increased. See HELP SLIMITS  
for details.

REGISTRY includes numerically searchable data for experimental and  
predicted properties as well as tags indicating availability of  
experimental property data in the original document. For information  
on property searching in REGISTRY, refer to:

<http://www.cas.org/ONLINE/UG/regprops.html>

FILE STNGUIDE  
FILE CONTAINS CURRENT INFORMATION.  
LAST RELOADED: Oct 7, 2005 (20051007/UP).

FILE HCAPLUS

Copyright of the articles to which records in this database refer is  
held by the publishers listed in the PUBLISHER (PB) field (available  
for records published or updated in Chemical Abstracts after December  
26, 1996), unless otherwise indicated in the original publications.  
The CA Lexicon is the copyrighted intellectual property of the  
the American Chemical Society and is provided to assist you in searching  
databases on STN. Any dissemination, distribution, copying, or storing  
of this information, without the prior written consent of CAS, is  
strictly prohibited.

FILE COVERS 1907 - 12 Oct 2005 VOL 143 ISS 16  
FILE LAST UPDATED: 11 Oct 2005 (20051011/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate  
substance identification.

FILE ZCAPLUS

Copyright of the articles to which records in this database refer is  
held by the publishers listed in the PUBLISHER (PB) field (available  
for records published or updated in Chemical Abstracts after December  
26, 1996), unless otherwise indicated in the original publications.  
The CA Lexicon is the copyrighted intellectual property of the  
American Chemical Society and is provided to assist you in searching  
databases on STN. Any dissemination, distribution, copying, or storing  
of this information, without the prior written consent of CAS is  
strictly prohibited.

FILE COVERS 1907 - 12 Oct 2005 VOL 143 ISS 16  
FILE LAST UPDATED: 11 Oct 2005 (20051011/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate  
substance identification.

FILE LREGISTRY  
LREGISTRY IS A STATIC LEARNING FILE

NEW CAS INFORMATION USE POLICIES, ENTER HELP USAGETERMS FOR DETAILS.

FILE TOXCENTER

FILE COVERS 1907 TO 11 Oct 2005 (20051011/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TOXCENTER has been enhanced with new files segments and search fields. See HELP CONTENT for more information.

TOXCENTER thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2005 vocabulary. See <http://www.nlm.nih.gov/mesh/> and [http://www.nlm.nih.gov/pubs/techbull1/nd04/nd04\\_mesh.html](http://www.nlm.nih.gov/pubs/techbull1/nd04/nd04_mesh.html) for a description of changes.

FILE USPATFULL

FILE COVERS 1971 TO PATENT PUBLICATION DATE: 11 Oct 2005 (20051011/PD)

FILE LAST UPDATED: 11 Oct 2005 (20051011/ED)

HIGHEST GRANTED PATENT NUMBER: US6954941

HIGHEST APPLICATION PUBLICATION NUMBER: US2005223461

CA INDEXING IS CURRENT THROUGH 11 Oct 2005 (20051011/UPCA)

ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 11 Oct 2005 (20051011/PD)

REVISED CLASS FIELDS (/NCL) LAST RELOADED: Aug 2005

USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Aug 2005

>>> USPAT2 is now available. USPATFULL contains full text of the original, i.e., the earliest published granted patents or applications. USPAT2 contains full text of the latest US publications, starting in 2001, for the inventions covered in USPATFULL. A USPATFULL record contains not only the original published document but also a list of any subsequent publications. The publication number, patent kind code, and publication date for all the US publications for an invention are displayed in the PI (Patent Information) field of USPATFULL records and may be searched in standard search fields, e.g., /PN, /PK, etc. <<<

>>> USPATFULL and USPAT2 can be accessed and searched together through the new cluster USPATALL. Type FILE USPATALL to enter this cluster. <<<

>>> Use USPATALL when searching terms such as patent assignees, classifications, or claims, that may potentially change from the earliest to the latest publication. <<<

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE WPIX

FILE LAST UPDATED: 11 OCT 2005 <20051011/UP>

MOST RECENT DERWENT UPDATE: 200565 <200565/DW>

DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

>>> FOR A COPY OF THE DERWENT WORLD PATENTS INDEX STN USER GUIDE, PLEASE VISIT:

[http://www.stn-international.de/training\\_center/patents/stn\\_guide.pdf](http://www.stn-international.de/training_center/patents/stn_guide.pdf) <<<

>>> FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES, SEE  
<http://thomsonderwent.com/coverage/latestupdates/> <<<

>>> FOR INFORMATION ON ALL DERWENT WORLD PATENTS INDEX USER  
 GUIDES, PLEASE VISIT:  
<http://thomsonderwent.com/support/userguides/> <<<

>>> NEW! FAST-ALERTING ACCESS TO NEWLY-PUBLISHED PATENT  
 DOCUMENTATION NOW AVAILABLE IN DERWENT WORLD PATENTS INDEX  
 FIRST VIEW - FILE WPIFV.  
 FOR FURTHER DETAILS: <http://www.thomsonderwent.com/dwpifv> <<<

>>> THE CPI AND EPI MANUAL CODES HAVE BEEN REVISED FROM UPDATE 200501.  
 PLEASE CHECK:  
<http://thomsonderwent.com/support/dwpiref/reftools/classification/code-rev>  
 FOR DETAILS. <<<

## FILE MEDLINE

FILE LAST UPDATED: 11 OCT 2005 (20051011/UP). FILE COVERS 1950 TO DATE.

On December 19, 2004, the 2005 MeSH terms were loaded.

The MEDLINE reload for 2005 is now available. For details enter HELP RLOAD at an arrow prompt (=&gt;). See also:

<http://www.nlm.nih.gov/mesh/>  
[http://www.nlm.nih.gov/pubs/techbull/nd04/nd04\\_mesh.html](http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html)

OLDMEDLINE now back to 1950.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2005 vocabulary.

This file contains CAS Registry Numbers for easy and accurate substance identification.

```
=> => d que l20
L11 ( 1)SEA FILE=WPIX ABB=ON PLU=ON (RADLBS/DCN OR RADLCX/DCN OR
      RADLCZ/DCN OR RADLD1/DCN OR RADLD3/DCN OR RADLD6/DCN OR
      RADL2W/DCN OR RADL2X/DCN OR RADL2Y/DCN OR RADL2Z/DCN OR
      RADL3C/DCN OR RADL3E/DCN OR RADL3J/DCN OR RADL3K/DCN OR
      RADL3W/DCN OR RADL3Y/DCN OR RADL3Z/DCN OR RADL3O/DCN OR
      RADL4D/DCN OR RADL4J/DCN OR RADL40/DCN OR RADL41/DCN OR
      RADL42/DCN OR RADL47/DCN OR RADL81/DCN OR RADL89/DCN OR
      0125-21301/DCN OR 0125-21302/DCN OR 0125-21303/DCN OR 0125-2130
      4/DCN OR 0125-21305/DCN OR 0125-21306/DCN OR 0125-21307/DCN OR
      0125-21308/DCN OR 0125-21309/DCN OR 0125-21310/DCN OR 0125-2131
      1/DCN OR 0125-21312/DCN OR 0125-21313/DCN OR 0125-21314/DCN)
L12 ( 27282)SEA FILE=WPIX ABB=ON PLU=ON ((D621 OR D622) (P) (G011 OR G012
      OR G013 OR G014 OR G015 OR G016 OR G221 OR F431 OR F541))/M0,M1
      ,M2,M3,M4,M5,M6
L13 ( 328)SEA FILE=WPIX ABB=ON PLU=ON (?HYDANTOI?/BIX OR ?HYDROXAM?/BIX
      ) (L) (MMP/BIX OR (?MATRIX?/BIX(2A) (?METALLOPROT?/BIX OR
      (?METALLO/BIX(1W) PROT?/BIX))) OR TNF/BIX OR ((?TUMOR?/BIX OR
      ?TUMOUR?/BIX) (2A) ?NECRO?/BIX) OR TACE/BIX OR (?ALPHA?/BIX(2A) (?CON
      VERT?/BIX OR ?CONVERS?/BIX)))
L14 ( 40)SEA FILE=WPIX ABB=ON PLU=ON (L11 OR L12) AND L13
L15 ( 3929)SEA FILE=WPIX ABB=ON PLU=ON (MMP/BIX OR (?MATRIX?/BIX(2A) (?MET
      ALLOPROT?/BIX OR (?METALLO/BIX(1W) PROT?/BIX))) OR TNF/BIX OR
```

((?TUMOR?/BIX OR ?TUMOUR?/BIX) (2A) ?NECRO?/BIX) OR TACE/BIX OR  
 (?ALPHA?/BIX (2A) (?CONVERT?/BIX OR ?CONVERS?/BIX))) (7A)  
 (?INHIBIT?/BIX OR ?REPRESS?/BIX OR ?SUPRESS?/BIX OR ?DISRUPT?/B  
 IX OR ?INTERRUPT?/BIX OR ?ANTAGON?/BIX OR ?PROHIBIT?/BIX OR  
 ?PREVENT?/BIX OR ?IMPED?/BIX OR ?REDUC?/BIX OR ?DEPRESS?/BIX  
 OR ?BLOCK?/BIX OR STOP?/BIX OR ?RETARD?/BIX OR SLOW?/BIX)  
 L16 ( 304) SEA FILE=WPIX ABB=ON PLU=ON L15 (L) (?HYDANTOI?/BIX OR  
 ?HYDROXAM?/BIX)  
 L17 38 SEA FILE=WPIX ABB=ON PLU=ON L14 AND L16  
 L19 196 SEA FILE=WPIX ABB=ON PLU=ON (?HYDANTOI?/BIX OR ?HYDROXAM?/BIX  
 ) (L) (?QUINOLIN?/BIX)  
 L20 14 SEA FILE=WPIX ABB=ON PLU=ON L17 AND L19

=> d que 131

L1 QUE ABB=ON PLU=ON ?HYDANTOI? OR ?HYDROXAM?  
 L6 QUE ABB=ON PLU=ON ?QUINOLIN?  
 L7 QUE ABB=ON PLU=ON ?PHENYL? OR ?BENZYL? OR ?NAPHTHYL? O  
 R ?NAPHTHENYL? OR ?PYRIDYL? OR ?PYRIDIN? OR ?PYRIMIDYL? O  
 R ?PYRIMIDIN? OR ?BENZENE?  
 L21 QUE ABB=ON PLU=ON MMP OR (?MATRIX? (2A) (?METALLOPROT? O  
 R (?METALLO(1W) PROT?))) OR TNF OR ((?TUMOR? OR ?TUMOUR?) (2A) ?NECRO?) OR TACE OR (?ALPHA? (2A) (?CONVERT? OR ?CONVERS?))  
 L23 15230 SEA FILE=MEDLINE ABB=ON PLU=ON HYDANTOINS+PFT,NT/CT  
 L24 485 SEA FILE=MEDLINE ABB=ON PLU=ON L23 (L) AA  
 L25 3 SEA FILE=MEDLINE ABB=ON PLU=ON L24 AND L21  
 L26 367 SEA FILE=MEDLINE ABB=ON PLU=ON L1 (L) L21  
 L27 970 SEA FILE=MEDLINE ABB=ON PLU=ON L1 (10A) (L6 OR L7)  
 L28 34 SEA FILE=MEDLINE ABB=ON PLU=ON L26 AND L27  
 L29 14 SEA FILE=MEDLINE ABB=ON PLU=ON L1 (7A) L6  
 L30 4 SEA FILE=MEDLINE ABB=ON PLU=ON L28 AND L29  
 L31 7 SEA FILE=MEDLINE ABB=ON PLU=ON L25 OR L30

=> d que 139

L1 QUE ABB=ON PLU=ON ?HYDANTOI? OR ?HYDROXAM?  
 L6 QUE ABB=ON PLU=ON ?QUINOLIN?  
 L7 QUE ABB=ON PLU=ON ?PHENYL? OR ?BENZYL? OR ?NAPHTHYL? O  
 R ?NAPHTHENYL? OR ?PYRIDYL? OR ?PYRIDIN? OR ?PYRIMIDYL? O  
 R ?PYRIMIDIN? OR ?BENZENE?  
 L21 QUE ABB=ON PLU=ON MMP OR (?MATRIX? (2A) (?METALLOPROT? O  
 R (?METALLO(1W) PROT?))) OR TNF OR ((?TUMOR? OR ?TUMOUR?) (2A) ?NECRO?) OR TACE OR (?ALPHA? (2A) (?CONVERT? OR ?CONVERS?))  
 L32 50409 SEA FILE=EMBASE ABB=ON PLU=ON "HYDANTOIN DERIVATIVE"+PFT,NT/C  
 T  
 L33 187 SEA FILE=EMBASE ABB=ON PLU=ON L32 AND L21  
 L36 391 SEA FILE=EMBASE ABB=ON PLU=ON L1 (L) L21  
 L37 17 SEA FILE=EMBASE ABB=ON PLU=ON L33 AND L36  
 L38 11 SEA FILE=EMBASE ABB=ON PLU=ON L37 AND (L6 OR L7)  
 L39 17 SEA FILE=EMBASE ABB=ON PLU=ON L37 OR L38

=> d his 147

(FILE 'BIOSIS, PASCAL, JICST-EPLUS, CABA, CANCERLIT, DRUGU, SCISEARCH'  
 ENTERED AT 08:16:50 ON 13 OCT 2005)  
 L47 53 DUP REM L46 (21 DUPLICATES REMOVED)

```
=> d que 147
L1      QUE ABB=ON PLU=ON ?HYDANTOI? OR ?HYDROXAM?
L6      QUE ABB=ON PLU=ON ?QUINOLIN?
L7      QUE ABB=ON PLU=ON ?PHENYL? OR ?BENZYL? OR ?NAPHTHYL? O
      R ?NAPHTHENYL? OR ?PYRIDYL? OR ?PYRIDIN? OR ?PYRIMIDYL? O
      R ?PYRIMIDIN? OR ?BENZENE?
L21     QUE ABB=ON PLU=ON MMP OR (?MATRIX?(2A)(?METALLOPROT? O
      R (?METALLO(1W)PROT?))) OR TNF OR ((?TUMOR? OR ?TUMOUR?)(2A)?NECRO?) OR TACE OR (?ALPHA?(2A)(?CONVERT? OR ?CONVERS?))
L40      6407 SEA L1 (7A) (L6 OR L7)
L41      20700 SEA L1/TI, IT, CC, CT, ST, STP
L42      4900 SEA L40 AND L41
L43      1538 SEA L1 (L) L21
L44      87 SEA L42 AND L43
L45      269429 SEA L21/TI, IT, CC, CT, ST, STP
L46      74 SEA L44 AND L45
L47      53 DUP REM L46 (21 DUPLICATES REMOVED)
```

=> d his 150

(FILE 'HCAPLUS, MEDLINE, BIOSIS, EMBASE, PASCAL, JICST-EPLUS, CABA, CANCERLIT, DRUGU, SCISEARCH, WPIX, CONF, CONFSCI, DISSABS' ENTERED AT 08:28:53 ON 13 OCT 2005)

```
L50      10 DUP REM L49 (3 DUPLICATES REMOVED)
```

=> d que 150

```
L1      QUE ABB=ON PLU=ON ?HYDANTOI? OR ?HYDROXAM?
L48      147 SEA MADUSKUIE, T?/AU
L49      13 SEA L48 AND L1
L50      10 DUP REM L49 (3 DUPLICATES REMOVED)
```

=> ~~d his ful~~

(FILE 'HOME' ENTERED AT 07:50:52 ON 13 OCT 2005)

FILE 'MEDLINE' ENTERED AT 07:51:03 ON 13 OCT 2005  
ACT HOF197MEDP/A

```
-----
L1      QUE ABB=ON PLU=ON ?HYDANTOI? OR ?HYDROXAM?
L2  (  501)SEA ABB=ON PLU=ON L1 (10A) L1
L3  (  15228)SEA ABB=ON PLU=ON HYDANTOINS+PFT,NT/CT
L4  (  485)SEA ABB=ON PLU=ON L3 (L) AA
L5  (  38)SEA ABB=ON PLU=ON L2 AND L4
L6      QUE ABB=ON PLU=ON ?QUINOLIN?
L7      QUE ABB=ON PLU=ON ?PHENYL? OR ?BENZYL? OR ?NAPHTHYL? OR
      ?NAPHTHENYL? OR ?PYRIDYL? OR ?PYRIDIN? OR ?PYRIMIDYL? OR
      ?PYRIMIDIN? OR ?BENZENE?
L8  (  4627)SEA ABB=ON PLU=ON L1 (L) (L6 OR L7)
L9      38 SEA ABB=ON PLU=ON L5 AND L8
-----
```

FILE 'STNGUIDE' ENTERED AT 07:51:12 ON 13 OCT 2005

FILE 'WPIX' ENTERED AT 07:52:15 ON 13 OCT 2005  
ACT HOF197WPIAPP/A

```
-----
L10     1 SEA ABB=ON PLU=ON US2003-632197/APPS
```

-----  
ACT HOF197WPIP/A  
-----

- L11 ( 1)SEA ABB=ON PLU=ON (RADLBS/DCN OR RADLCX/DCN OR RADLCZ/DCN OR RADLD1/DCN OR RADLD3/DCN OR RADLD6/DCN OR RADL2W/DCN OR RADL2X/DCN OR RADL2Y/DCN OR RADL2Z/DCN OR RADL3C/DCN OR RADL3E/DCN OR RADL3J/DCN OR RADL3K/DCN OR RADL3W/DCN OR RADL3Y/DCN OR RADL3Z/DCN OR RADL30/DCN OR RADL4D/DCN OR RADL4J/DCN OR RADL40/DCN OR RADL41/DCN OR RADL42/DCN OR RADL47/DCN OR RADL81/DCN OR RADL89/DCN OR 0125-21301/DCN OR 0125-21302/DCN OR 0125-21303/DCN OR 0125-21304/DCN OR 0125-21305/DCN OR 0125-21306/DCN OR 0125-21307/DCN OR 0125-21308/DCN OR 0125-21309/DCN OR 0125-21310/DCN OR 0125-21311/DCN OR 0125-21312/DCN OR 0125-21313/DCN OR 0125-21314/DCN)
- L12 ( 27282)SEA ABB=ON PLU=ON ((D621 OR D622)(P) (G011 OR G012 OR G013 OR G014 OR G015 OR G016 OR G221 OR F431 OR F541))/M0,M1,M2,M3,M4,M5,M6
- L13 ( 328)SEA ABB=ON PLU=ON (?HYDANTOI?/BIX OR ?HYDROXAM?/BIX) (L) (MMP/BIX OR (?MATRIX?/BIX(2A) (?METALLOPROT?/BIX OR (?METALLO/BIX(1W) PROT?/BIX))) OR TNF/BIX OR ((?TUMOR?/BIX OR ?TUMOUR?/BIX)(2A) ?NECRO?/BIX) OR TACE/BIX OR (?ALPHA?/BIX(2A) (?CONVERT?/BIX OR ?CONVERS?/BIX)))
- L14 ( 40)SEA ABB=ON PLU=ON (L11 OR L12) AND L13
- L15 ( 3929)SEA ABB=ON PLU=ON (MMP/BIX OR (?MATRIX?/BIX(2A) (?METALLOPROT?/BIX OR (?METALLO/BIX(1W) PROT?/BIX))) OR TNF/BIX OR ((?TUMOR?/BIX OR ?TUMOUR?/BIX)(2A) ?NECRO?/BIX) OR TACE/BIX OR (?ALPHA?/BIX(2A) (?CONVERT?/BIX OR ?CONVERS?/BIX))) (7A) (?INHIBIT?/BIX OR ?REPRESS?/BIX OR ?SUPRESS?/BIX OR ?DISRUPT?/BIX OR ?INTERRUPT?/BIX OR ?ANTAGON?/BIX OR ?PROHIBIT?/BIX OR ?PREVENT?/BIX OR ?IMPED?/BIX OR ?REDUC?/BIX OR ?DEPRESS?/BIX OR ?BLOCK?/BIX OR STOP?/BIX OR ?RETARD?/BIX OR SLOW?/BIX)
- L16 ( 304)SEA ABB=ON PLU=ON L15 (L) (?HYDANTOI?/BIX OR ?HYDROXAM?/BIX)

L17 38 SEA ABB=ON PLU=ON L14 AND L16

-----  
D QUE

FILE 'STNGUIDE' ENTERED AT 07:53:01 ON 13 OCT 2005

FILE 'HCAPLUS' ENTERED AT 07:56:05 ON 13 OCT 2005

FILE 'STNGUIDE' ENTERED AT 07:56:21 ON 13 OCT 2005

FILE 'HCAPLUS' ENTERED AT 07:56:44 ON 13 OCT 2005

FILE 'STNGUIDE' ENTERED AT 07:56:54 ON 13 OCT 2005

L18 QUE ABB=ON PLU=ON MMP OR (?MATRIX?(2A) (?METALLOPROT? OR (?METALLO(1W) PROT?))) OR TNF OR ((?TUMOR? OR ?TUMOUR?)(2A) ?NECRO?) OR TACE OR (?ALPHA?(2A) (?CONVERT? OR ?CONVERS?))

FILE 'STNGUIDE' ENTERED AT 07:57:41 ON 13 OCT 2005

D QUE L17

FILE 'WPIX' ENTERED AT 07:58:07 ON 13 OCT 2005

L19 196 SEA ABB=ON PLU=ON (?HYDANTOI?/BIX OR ?HYDROXAM?/BIX) (L) (?QUINOLIN?/BIX)

L20 14 SEA ABB=ON PLU=ON L17 AND L19

FILE 'HCAPLUS' ENTERED AT 08:02:33 ON 13 OCT 2005

L21 QUE ABB=ON PLU=ON MMP OR (?MATRIX?(2A) (?METALLOPROT? OR

(?METALLO(1W)PROT?))) OR TNF OR ((?TUMOR? OR ?TUMOUR?),(2A)?NECR  
O?) OR TACE OR (?ALPHA?(2A)(?CONVERT? OR ?CONVERS?))

FILE 'STNGUIDE' ENTERED AT 08:02:41 ON 13 OCT 2005

FILE 'WPIX' ENTERED AT 08:02:47 ON 13 OCT 2005  
D TRI L20 1-14

FILE 'STNGUIDE' ENTERED AT 08:03:09 ON 13 OCT 2005

FILE 'WPIX' ENTERED AT 08:04:55 ON 13 OCT 2005  
SAVE TEMP L20 HOF197WPI1/A

FILE 'STNGUIDE' ENTERED AT 08:05:10 ON 13 OCT 2005  
D SAVED

FILE 'MEDLINE' ENTERED AT 08:05:34 ON 13 OCT 2005  
D QUE L9

L22	0 SEA ABB=ON	PLU=ON	L9 AND L21
L23	15230 SEA ABB=ON	PLU=ON	HYDANTOINS+PFT,NT/CT
L24	485 SEA ABB=ON	PLU=ON	L23 (L) AA
L25	3 SEA ABB=ON	PLU=ON	L24 AND L21
L26	367 SEA ABB=ON	PLU=ON	L1 (L) L21
L27	970 SEA ABB=ON	PLU=ON	L1 (10A) (L6 OR L7)
L28	34 SEA ABB=ON	PLU=ON	L26 AND L27
L29	14 SEA ABB=ON	PLU=ON	L1 (7A) L6
L30	4 SEA ABB=ON	PLU=ON	L28 AND L29
L31	7 SEA ABB=ON	PLU=ON	L25 OR L30

D TRI 1-7

FILE 'STNGUIDE' ENTERED AT 08:08:34 ON 13 OCT 2005

FILE 'MEDLINE' ENTERED AT 08:09:30 ON 13 OCT 2005  
D KWIC 1-7

FILE 'STNGUIDE' ENTERED AT 08:09:30 ON 13 OCT 2005

FILE 'MEDLINE' ENTERED AT 08:09:46 ON 13 OCT 2005  
D TI KWIC 1-7

FILE 'STNGUIDE' ENTERED AT 08:09:46 ON 13 OCT 2005

FILE 'STNGUIDE' ENTERED AT 08:09:51 ON 13 OCT 2005

FILE 'MEDLINE' ENTERED AT 08:10:55 ON 13 OCT 2005  
SAVE TEMP L31 HOF197MED1/A

FILE 'STNGUIDE' ENTERED AT 08:11:11 ON 13 OCT 2005

FILE 'EMBASE' ENTERED AT 08:11:14 ON 13 OCT 2005  
E HYDANTOIN/CT

L32	50409 SEA ABB=ON	PLU=ON	"HYDANTOIN DERIVATIVE"+PFT,NT/CT
L33	187 SEA ABB=ON	PLU=ON	L32 AND L21
L34	17 SEA ABB=ON	PLU=ON	L1 (10A) L6
L35	0 SEA ABB=ON	PLU=ON	L33 AND L34
L36	391 SEA ABB=ON	PLU=ON	L1 (L) L21
L37	17 SEA ABB=ON	PLU=ON	L33 AND L36

D TRI 1-17

FILE 'STNGUIDE' ENTERED AT 08:13:08 ON 13 OCT 2005

L38 FILE 'EMBASE' ENTERED AT 08:14:44 ON 13 OCT 2005  
 L38       11 SEA ABB=ON PLU=ON L37 AND (L6 OR L7)  
 L39       17 SEA ABB=ON PLU=ON L37 OR L38  
 L39       SAVE TEMP L39 HOF197EMB1/A

FILE 'STNGUIDE' ENTERED AT 08:15:21 ON 13 OCT 2005  
 D SAVED

FILE 'BIOSIS, PASCAL, JICST-EPLUS, CABA, CANCERLIT, DRUGU, SCISEARCH'  
 ENTERED AT 08:16:50 ON 13 OCT 2005  
 L40       6407 SEA ABB=ON PLU=ON L1 (7A) (L6 OR L7)  
 L41       20700 SEA ABB=ON PLU=ON L1/TI, IT, CC, CT, ST, STP  
 L42       4900 SEA ABB=ON PLU=ON L40 AND L41  
 L43       1538 SEA ABB=ON PLU=ON L1 (L) L21  
 L44       87 SEA ABB=ON PLU=ON L42 AND L43  
 L45       269429 SEA ABB=ON PLU=ON L21/TI, IT, CC, CT, ST, STP  
 L46       74 SEA ABB=ON PLU=ON L44 AND L45  
 L47       53 DUP REM L46 (21 DUPLICATES REMOVED)  
 L47       ANSWERS '1-19' FROM FILE BIOSIS  
 L47       ANSWERS '20-42' FROM FILE PASCAL  
 L47       ANSWER '43' FROM FILE CANCERLIT  
 L47       ANSWERS '44-45' FROM FILE DRUGU  
 L47       ANSWERS '46-53' FROM FILE SCISEARCH  
 L47       SAVE TEMP L47 HOF197MULT1/A  
 L47       D SAVED

FILE 'STNGUIDE' ENTERED AT 08:27:37 ON 13 OCT 2005

FILE 'HCAPLUS, MEDLINE, BIOSIS, EMBASE, PASCAL, JICST-EPLUS, CABA,  
 CANCERLIT, DRUGU, SCISEARCH, WPIX, CONF, CONFSCI, DISSABS' ENTERED AT  
 08:28:53 ON 13 OCT 2005  
 L48       147 SEA ABB=ON PLU=ON MADUSKUIE, T?/AU  
 L49       13 SEA ABB=ON PLU=ON L48 AND L1  
 L50       10 DUP REM L49 (3 DUPLICATES REMOVED)  
 L50       ANSWERS '1-6' FROM FILE HCAPLUS  
 L50       ANSWER '7' FROM FILE BIOSIS  
 L50       ANSWERS '8-9' FROM FILE DRUGU  
 L50       ANSWER '10' FROM FILE SCISEARCH  
 L50       SAVE TEMP L50 HOF197MULINV/A  
 L50       D SAVED

FILE 'STNGUIDE' ENTERED AT 08:30:44 ON 13 OCT 2005

FILE 'HCAPLUS' ENTERED AT 08:31:12 ON 13 OCT 2005

FILE 'MEDLINE' ENTERED AT 08:31:18 ON 13 OCT 2005

FILE 'WPIX' ENTERED AT 08:31:28 ON 13 OCT 2005

FILE 'EMBASE' ENTERED AT 08:31:32 ON 13 OCT 2005

FILE 'BIOSIS' ENTERED AT 08:31:35 ON 13 OCT 2005

FILE 'PASCAL' ENTERED AT 08:31:39 ON 13 OCT 2005

FILE 'JICST-EPLUS' ENTERED AT 08:31:42 ON 13 OCT 2005

FILE 'CABA' ENTERED AT 08:31:45 ON 13 OCT 2005

Hoffman 10/632,197

10/13/2005

FILE 'CANCERLIT' ENTERED AT 08:31:49 ON 13 OCT 2005

FILE 'DRUGU' ENTERED AT 08:31:53 ON 13 OCT 2005

FILE 'SCISEARCH' ENTERED AT 08:31:58 ON 13 OCT 2005

FILE 'CONF' ENTERED AT 08:32:00 ON 13 OCT 2005

FILE 'CONFSCI' ENTERED AT 08:32:09 ON 13 OCT 2005

FILE 'DISSABS' ENTERED AT 08:32:14 ON 13 OCT 2005

FILE 'STNGUIDE' ENTERED AT 08:32:16 ON 13 OCT 2005

D QUE L20

D QUE L31

D QUE L39

D QUE L47

FILE 'WPIX, MEDLINE, EMBASE, BIOSIS, PASCAL, CANCERLIT, DRUGU, SCISEARCH'  
ENTERED AT 08:33:16 ON 13 OCT 2005

L51 85 DUP REM L20 L31 L39 L47 (6 DUPLICATES REMOVED)

ANSWERS '1-14' FROM FILE WPIX

ANSWERS '15-21' FROM FILE MEDLINE

ANSWERS '22-37' FROM FILE EMBASE

ANSWERS '38-53' FROM FILE BIOSIS

ANSWERS '54-75' FROM FILE PASCAL

ANSWER '76' FROM FILE CANCERLIT

ANSWERS '77-78' FROM FILE DRUGU

ANSWERS '79-85' FROM FILE SCISEARCH

FILE 'STNGUIDE' ENTERED AT 08:33:24 ON 13 OCT 2005

FILE 'WPIX, MEDLINE, EMBASE, BIOSIS, PASCAL, CANCERLIT, DRUGU, SCISEARCH'  
ENTERED AT 08:33:45 ON 13 OCT 2005

D IALL ABEQ TECH ABEX

FILE 'STNGUIDE' ENTERED AT 08:33:47 ON 13 OCT 2005

FILE 'WPIX, MEDLINE, EMBASE, BIOSIS, PASCAL, CANCERLIT, DRUGU, SCISEARCH'  
ENTERED AT 08:34:40 ON 13 OCT 2005

D IALL ABEQ TECH ABEX 2-14

FILE 'STNGUIDE' ENTERED AT 08:34:50 ON 13 OCT 2005

FILE 'WPIX, MEDLINE, EMBASE, BIOSIS, PASCAL, CANCERLIT, DRUGU, SCISEARCH'  
ENTERED AT 08:35:33 ON 13 OCT 2005

D IBIB ED AB HITIND 15-

FILE 'STNGUIDE' ENTERED AT 08:35:54 ON 13 OCT 2005

D QUE L50

FILE 'HCAPLUS, BIOSIS, DRUGU, SCISEARCH' ENTERED AT 08:37:05 ON 13 OCT  
2005

D IBIB ED AB L50 1-10

FILE 'STNGUIDE' ENTERED AT 08:37:07 ON 13 OCT 2005

FILE 'STNGUIDE' ENTERED AT 08:37:18 ON 13 OCT 2005

D QUE L20

D QUE L31

D QUE L39  
D QUE L47  
D QUE L50

**FILE HOME****FILE MEDLINE**

FILE LAST UPDATED: 12 OCT 2005 (20051012/UP). FILE COVERS 1950 TO DATE.

On December 19, 2004, the 2005 MeSH terms were loaded.

The MEDLINE reload for 2005 is now available. For details enter HELP RLOAD at an arrow prompt (=>). See also:

<http://www.nlm.nih.gov/mesh/>  
[http://www.nlm.nih.gov/pubs/techbull/nd04/nd04\\_mesh.html](http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html)

OLDMEDLINE now back to 1950.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2005 vocabulary.

This file contains CAS Registry Numbers for easy and accurate substance identification.

**FILE STNGUIDE**

FILE CONTAINS CURRENT INFORMATION.

LAST RELOADED: Oct 7, 2005 (20051007/UP).

**FILE WPIX**

FILE LAST UPDATED: 11 OCT 2005 <20051011/UP>  
MOST RECENT DERWENT UPDATE: 200565 <200565/DW>  
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

>>> FOR A COPY OF THE DERWENT WORLD PATENTS INDEX STN USER GUIDE,  
PLEASE VISIT:  
[<<<](http://www.stn-international.de/training_center/patents/stn_guide.pdf)

>>> FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES, SEE  
<http://thomsonderwent.com/coverage/latestupdates/> <<<

>>> FOR INFORMATION ON ALL DERWENT WORLD PATENTS INDEX USER  
GUIDES, PLEASE VISIT:  
<http://thomsonderwent.com/support/userguides/> <<<

>>> NEW! FAST-ALERTING ACCESS TO NEWLY-PUBLISHED PATENT  
DOCUMENTATION NOW AVAILABLE IN DERWENT WORLD PATENTS INDEX  
FIRST VIEW - FILE WPIFV.  
FOR FURTHER DETAILS: [<<<](http://www.thomsonderwent.com/dwpifv)

>>> THE CPI AND EPI MANUAL CODES HAVE BEEN REVISED FROM UPDATE 200501.  
PLEASE CHECK:  
<http://thomsonderwent.com/support/dwpiref/reftools/classification/code-rev>  
FOR DETAILS. <<<

**FILE HCAPLUS**

Copyright of the articles to which records in this database refer is held by the publishers listed in the PUBLISHER (PB) field (available

for records published or updated in Chemical Abstracts after December 26, 1996), unless otherwise indicated in the original publications. The CA Lexicon is the copyrighted intellectual property of the American Chemical Society and is provided to assist you in searching databases on STN. Any dissemination, distribution, copying, or storing of this information, without the prior written consent of CAS, is strictly prohibited.

FILE COVERS 1907 - 13 Oct 2005 VOL 143 ISS 16  
FILE LAST UPDATED: 12 Oct 2005 (20051012/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE EMBASE  
FILE COVERS 1974 TO 6 Oct 2005 (20051006/ED)

EMBASE has been reloaded. Enter HELP RLOAD for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE BIOSIS  
FILE COVERS 1969 TO DATE.  
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNS) PRESENT  
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 12 October 2005 (20051012/ED)

FILE RELOADED: 19 October 2003.

FILE PASCAL  
FILE LAST UPDATED: 10 OCT 2005 <20051010/UP>  
FILE COVERS 1977 TO DATE.

>>> SIMULTANEOUS LEFT AND RIGHT TRUNCATION IS AVAILABLE  
IN THE BASIC INDEX (/BI) FIELD <<<

FILE JICST-EPLUS  
FILE COVERS 1985 TO 12 OCT 2005 (20051012/ED)

THE JICST-EPLUS FILE HAS BEEN RELOADED TO REFLECT THE 1999 CONTROLLED TERM (/CT) THESAURUS RELOAD.

FILE CABA  
FILE COVERS 1973 TO 7 Oct 2005 (20051007/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

The CABA file was reloaded 7 December 2003. Enter HELP RLOAD for details.

FILE CANCERLIT  
FILE COVERS 1963 TO 15 Nov 2002 (20021115/ED)

On July 28, 2002, CANCERLIT was reloaded. See HELP RLOAD for details.

CANCERLIT thesauri in the /CN, /CT, and /MN fields incorporate the

MeSH 2002 vocabulary. Enter HELP THESAURUS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE DRUGU  
FILE LAST UPDATED: 11 OCT 2005 <20051011/UP>  
>>> DERWENT DRUG FILE (SUBSCRIBER) <<<  
  
>>> FILE COVERS 1983 TO DATE <<<  
>>> THESAURUS AVAILABLE IN /CT <<<

FILE SCISEARCH

FILE COVERS 1974 TO 6 Oct 2005 (20051006/ED)

SCISEARCH has been reloaded, see HELP RLOAD for details.

FILE CONF  
FILE LAST UPDATED: 7 OCT 2005 <20051007/UP>  
FILE COVERS 1976 TO DATE.

FILE CONFSCI  
FILE COVERS 1973 TO 25 May 2005 (20050525/ED)

FILE DISSABS  
FILE COVERS 1861 TO 29 SEP 2005 (20050929/ED)

Only fair use as provided by the United States copyright law is permitted. PROQUEST INFORMATION AND LEARNING COMPANY MAKES NO WARRANTY REGARDING THE ACCURACY, COMPLETENESS OR TIMELINESS OF THE LICENSED MATERIALS OR ANY WARRANTY, EXPRESS OR IMPLIED, INCLUDING ANY WARRANTY OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE, AND SHALL NOT BE LIABLE FOR DAMAGES OF ANY KIND OR LOST PROFITS OR OTHER CLAIMS RELATED TO THE LICENSED MATERIALS OR THEIR USE.

=>